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| (21) International Application Number: PCT/US98/00619 (22) International Filing Date: 13 January 1998 (13.01.98) (30) Priority Data: 60/036,183 17 January 1997 (17.01.97) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventors: GREGG, Richard, E.; 7 Linden Lane, Pennington, NJ 08534 (US). WETTERAU, John, R., II; 190 Rugby Drive, Langhorne, PA 19047 (US). (74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Com- pany, P.O. Box 4000, Princeton, NJ 08543-4000 (US). | | (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: METHOD FOR TREATING ACID LIPASE DEFICIENCY DISEASES WITH AN MTP INHIBITOR AND CHOLESTEROL LOWERING DRUGS (57) Abstract A method is provided for inhibiting or treating diseases associated with acid lipase deficiency by administering to a patient an MTP inhibitor, alone or optionally, in combination with another cholesterol lowering drug, such as pravastatin. | | |

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METHOD FOR TREATING ACID LIPASE DEFICIENCY DISEASES WITH AN MTP INHIBITOR AND CHOLESTEROL LOWERING DRUGS

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Field of the Invention

The present invention related to a method for inhibiting or treating diseases associated with acid lipase deficiency, including Wolman disease and/or cholesteryl ester storage disease, by administering an MTP inhibitor alone or in combination with another cholesterol lowering drug, such as pravastatin.

Background of the Invention

15 Wolman disease and cholesteryl ester storage disease are characterized by a deficiency in activity of lysosomal acid lipase which results in massive accumulation of cholesteryl esters and triglycerides in most tissues of the body. Cholesteryl esters and triglycerides are derived from plasma lipoproteins taken up by the cells and are substrates for acid lipase. Acid lipase is responsible for the hydrolysis of cholesteryl esters and triglycerides in the lysosomes.

20 If plasma cholesterol levels are lowered sufficiently, then cholesteryl ester and triglyceride accumulation in the lysosomes and the consequences of the accumulation could be minimized.

 Wolman disease is the more severe of the two diseases and is almost always fatal before the age of 1 year. In contrast, cholesteryl ester storage disease may go undetected until adulthood by which time lipid deposition is widespread. Hyperbetalipoproteinemia is common in cholesteryl ester storage disease, and premature atherosclerosis may be severe.

30 To date, there has been no specific therapy for acid lipase deficiency other than attempts at suppression of cholesterol synthesis and apolipoprotein B production by

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in combination with cholestyramine treatment and a diet excluding foods rich in cholesterol and triglycerides. The above apparently provided improvement in only one or two cases of cholesteryl ester storage disease. Thus, for the most part, Wolman disease and cholesteryl ester storage disease have been untreatable.

See Scriver, C.R. et al "The Metabolic and Molecular Bases of Inherited Disease", Vol. II (1995), Chap. 82, "Acid Lipase Deficiency: Wolman Disease and Cholesteryl Ester Storage Disease", pp. 2563-2587.

Until now, there have not been any therapeutic agents available which could lower plasma cholesterol levels sufficiently to minimize cholesteryl ester and triglyceride accumulation in the lysosomes.

The microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride (TG), cholesteryl ester (CE), and phosphatidylcholine (PC) between small unilamellar vesicles (SUV). Wetterau & Zilversmit, Chem. Phys. Lipids 38, 205-22 (1985). When transfer rates are expressed as the percent of the donor lipid transferred per time, MTP expresses a distinct preference for neutral lipid transport (TG and CE), relative to phospholipid transport. The microsomal triglyceride transfer protein from bovine liver has been isolated and extensively characterized (1). This has led to the cloning of cDNA expressing the protein from several species, including humans (2). MTP is composed of two subunits. The small subunit is the previously characterized multifunctional protein, protein disulfide isomerase. This is supported by biochemical analysis of the protein (3) as well as co-expression studies performed in insect Sf9 cells using the baculovirus expression system. Expression of soluble active MTP requires the co-expression of PDI and the unique large subunit of MTP (4).

- 1: Wetterau, J.R. and Zilversmit, D.B. (1985) Chem. Phys. Lipids 38, 205-222.
- Wetterau, J.R., et al, (1990) J. Biol. Chem. 265, 9800-9807.
- 5 Wetterau, J.R., et al, (1991) Biochemistry 30, 4406-4412.
- Atzel, A., and Wetterau, J.R. (1993) Biochemistry 32, 10444-10450.
- Atzel, A., and Wetterau, J.R. (1994) Biochemistry 10 33, 15382-15388.
- Jamil, H., et al, (1995) J. Biol. Chem. 270, 6549-6554.
2. Sharp, D. et al, (1993) Nature 365, 65-69.
- 15 Lin, M.C.M., et al, J. Biol. Chem. 269, 29138-29145.
- Nakamuta, M., et al, (1996) Genomics 33, 313-316.
3. Wetterau, J.R., et al, (1990) J. Biol. Chem. 265, 9800-9807.
- 20 Wetterau, J.R., et al, (1991) Biochemistry 30, 9728-9735.
4. Ricci, B., et al, (1995) J. Biol. Chem. 270, 14281-14285.

25

In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes. Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). The ability of

30 MTP to catalyze the transport of TG between membranes is consistent with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in

the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain apolipoprotein B (apoB). Kane & Havel in The Metabolic Basis of Inherited Disease, Sixth edition, 1139-64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are often only 20-45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect had not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are free of atherosclerosis. Schaefer et al., Clin. Chem. 34, B9-12 (1988). A link between the apoB gene and abetalipoproteinemia has been excluded in several families. Talmud et al., J. Clin. Invest. 82, 1803-6 (1988) and Huang et al., Am. J. Hum. Genet. 46, 1141-8 (1990).

Recent reports (5) demonstrate that the defect causing abetalipoproteinemia is in the MTP gene, and as a result, the MTP protein. When examined, individuals with abetalipoproteinemia have no MTP activity, as a result of mutations in the MTP gene, some of which have been characterized. These results indicate that MTP is required for the synthesis of apoB containing lipoproteins, such as VLDL, the precursor to LDL. It therefore follows that inhibitors of MTP would inhibit the synthesis of VLDL and LDL, thereby lowering VLDL levels, LDL levels, cholesterol levels, and triglyceride levels in animals and man.

5. Wetterau, J.R., et al, (1992) Science 258, 999-1001.
- 35 Sharp, D., et al, (1993) Nature 365, 65-69.
- Ricci, B., et al, (1995) J. Biol. Chem. 270, 14281-14285.

Shoulders, C.C., et al, (1993) Hum. Mol. Genetics
2, 2109-2116.

Narcisi, T.M.E., et al, (1995) Am. J. Hum. Genet.
57, 1298-1310.

5 Rehberg, E.F., et al, J. Biol. Chem (in press)..

Canadian Patent Application No. 2,091,102 published
March 2, 1994 (corresponding to U.S. application Serial No.
117,362, filed September 3, 1993 (file DC21b)) which is
10 incorporated herein by reference), reports MTP inhibitors
which also block apoB containing lipoprotein secretion in a
human hepatic cell line (HepG2 cells). This provides
further support for the proposal that an MTP inhibitor
would lower apoB containing lipoprotein and lipid levels in
15 vivo. This Canadian patent application discloses a method
for identifying the MTP inhibitors.

The use of microsomal triglyceride transfer protein
(MTP) inhibitors for decreasing serum lipids including
cholesterol and triglycerides and their use in treating
20 atherosclerosis, obesity, hyperglycemia, and pancreatitis
is disclosed in WO 96/26205, published August 29, 1996,
U.S. Application Serial No. 472,067, filed June 6, 1995
(file DC21e), U.S. Application Serial No. 548,811, filed
January 11, 1996 (file DC21h), U.S. provisional application
25 No. 60/017,224, filed May 9, 1996 (file HX79a*), U.S.
provisional application No. 60/017,253, filed May 10, 1996
(file HX82*), U.S. provisional application No. 60/017,254,
May 10, 1996 (file HX84*) and U.S. provisional application
No. 60/028,216, filed October 1, 1996 (file HX86*).

30 All of the above U.S. applications are incorporated
herein by reference.

Description of the Invention

In accordance with the present invention, a method
35 is provided for inhibiting or treating a disease associated
with acid lipase deficiency, including Wolman disease
and/or cholesteryl ester storage disease (CESD), in

mammalian species, wherein a therapeutically effective amount of a microsomal triglyceride transfer protein (MTP) inhibitor is administered to a patient in need of treatment.

5 The MTP inhibitor may optionally be administered in combination with another cholesterol lowering drug or delipidating agent.

 The MTP inhibitor alone or optionally in combination with another cholesterol lowering drug is administered
10 systemically, such as orally or parenterally or transdermally, to patients in need of treatment.

 In accordance with the present invention, the MTP inhibitor lowers plasma cholesterol (LDL-cholesterol) to at least about 50% of normal LDL blood level, preferably down
15 to less than about 25% of normal, and most preferably down to less than about 15% of normal, and lowers triglycerides to at least about 50% of normal triglyceride blood level, and preferably down to about 25% or less of normal, and thereby minimizes cholesteryl ester and triglyceride
20 accumulation in the lysosomes.

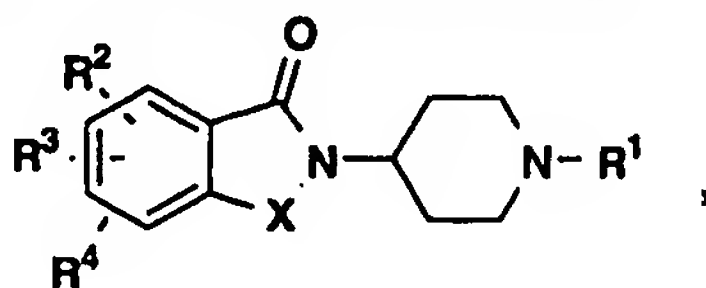
 The terms "another cholesterol lowering drug or agent" or "another delipidating drug" will be employed interchangeably herein.

 MTP inhibitors to be employed in the methods of the
25 invention include MTP inhibitors disclosed in Canadian Patent Application No. 2,091,102 described hereinbefore (corresponding to U.S. Application Serial No. 117,362), WO 92/26205 published August 29, 1996, U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e), U.S.
30 Application Serial No. 548,811, filed January 11, 1996 (file DC21h), U.S. provisional application No. 60/017,224, filed May 9, 1996 (file HX79a*), U.S. provisional application No. 60/017,253, filed May 10, 1996 (file HX82*), U.S. provisional application No. 60/017,254, filed
35 May 10, 1996 (file HX84*), and U.S. provisional application No. 60/028,216, filed October 1, 1996 (file HX86*).

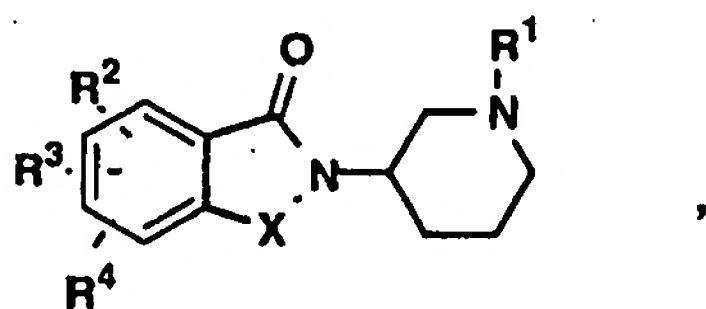
Preferred are each of the preferred MTP inhibitors disclosed in each of the above applications.

All of the above U.S. applications are incorporated herein by reference.

- 5 The MTP inhibitors disclosed in U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e) are piperidine compounds of the structure

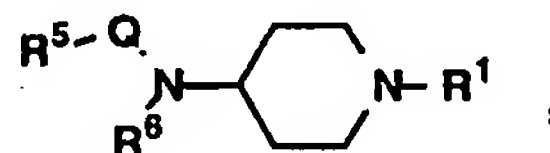


or

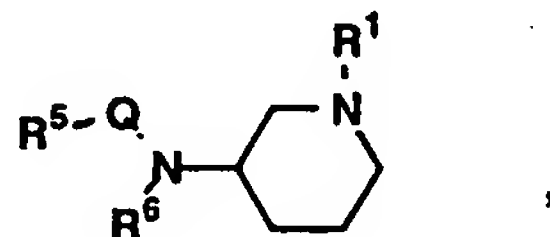


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or

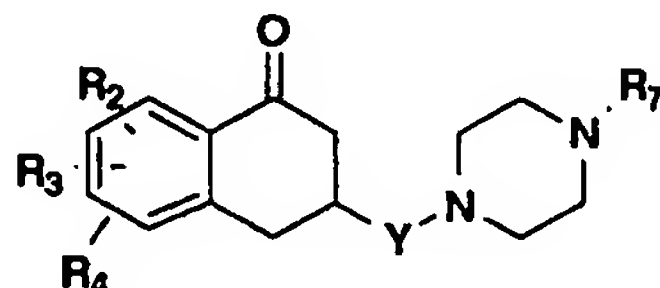


or



15

or



where Q is $\text{—}\overset{\text{O}}{\parallel}\text{C—}$ or $\text{—}\overset{\text{O}}{\parallel}\text{S—}$;

20 X is: CHR^8 , $\text{—}\overset{\text{O}}{\parallel}\text{C—}$, $\text{—}\underset{\text{R}^9}{\text{CH}}\text{—}\underset{\text{R}^{10}}{\text{CH}}\text{—}$ or $\text{—}\underset{\text{R}^9}{\text{C}}=\underset{\text{R}^{10}}{\text{C}}\text{—}$;

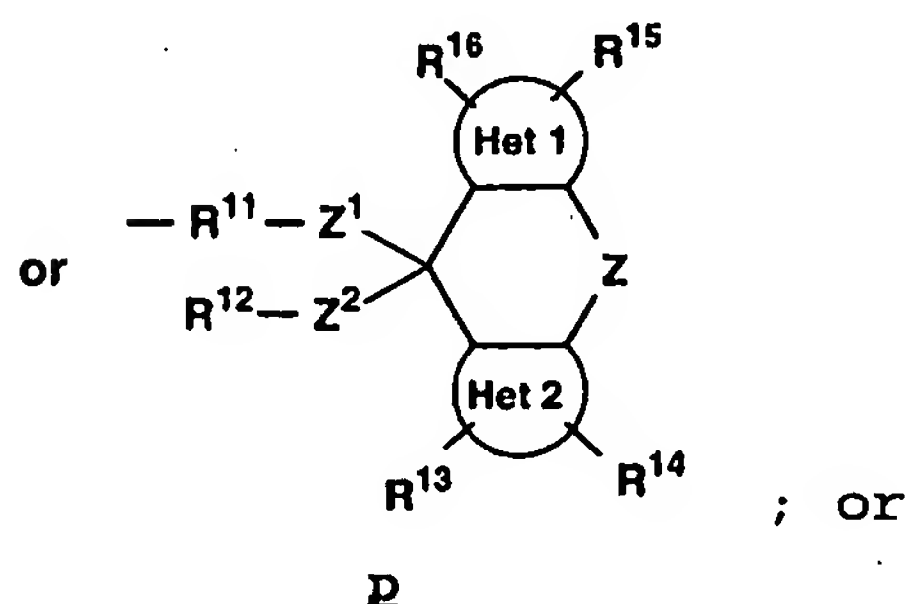
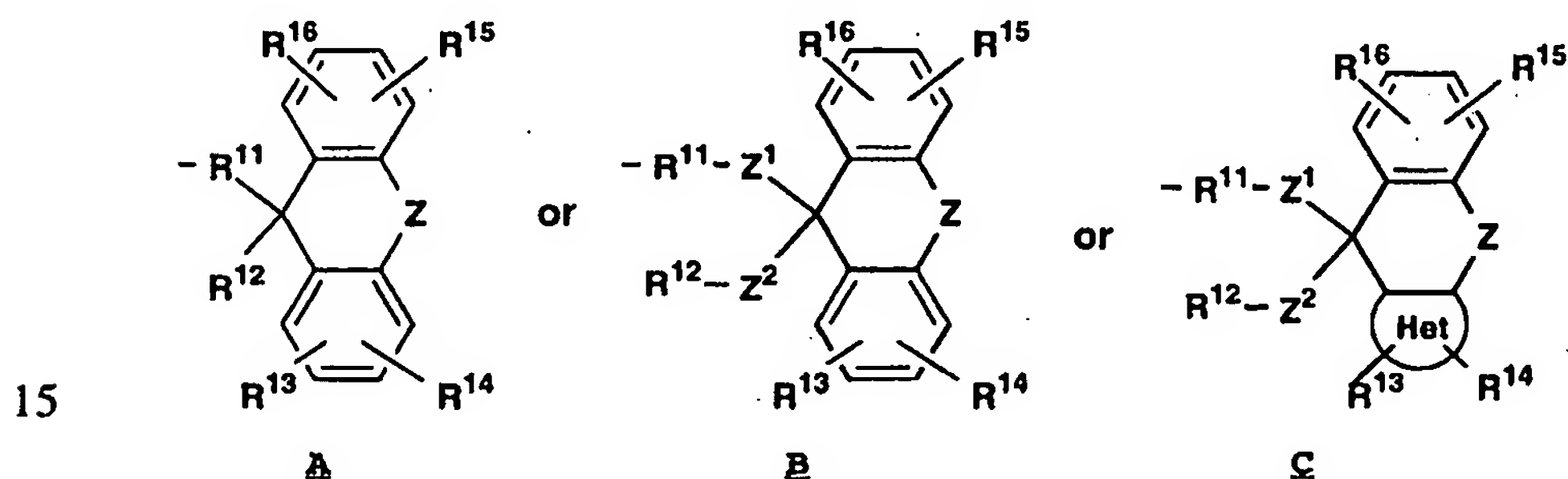
R^8 , R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

25 Y is $\text{—}(\text{CH}_2)_m\text{—}$ or $\text{—}\overset{\text{O}}{\parallel}\text{C—}$

wherein m is 2 or 3;

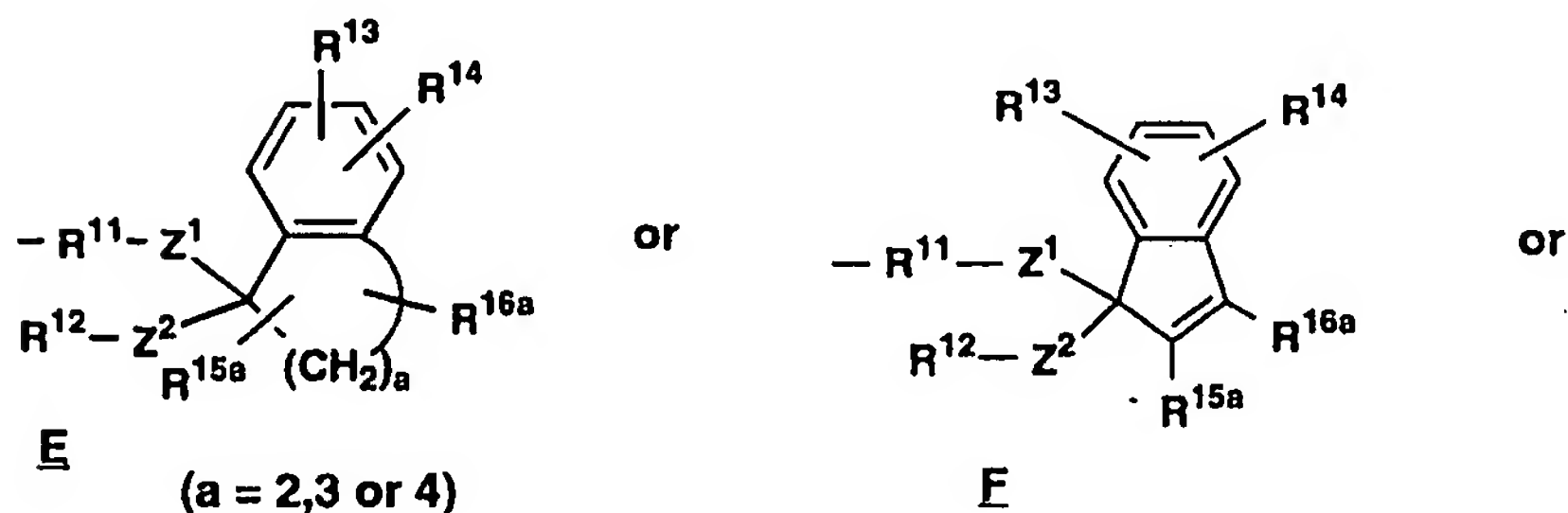
R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, 5 diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, 10 alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

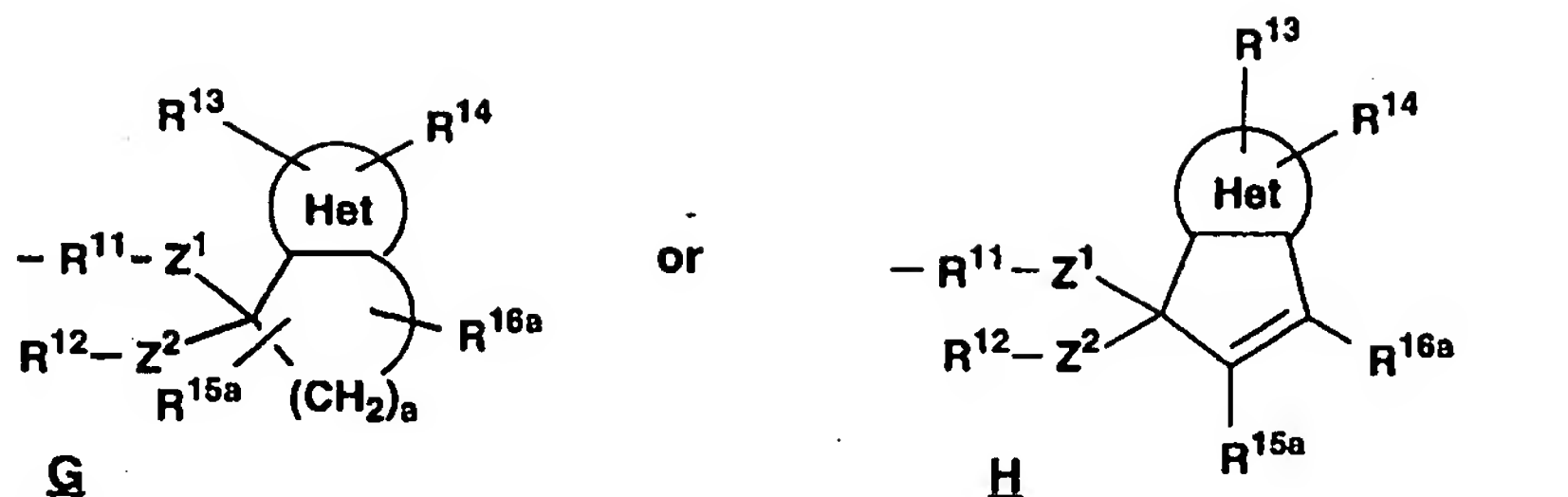
or R^1 is a fluorenyl-type group of the structure



20

R^1 is an indenyl-type group of the structure





Z^1 and Z^2 are the same or different and are independently a bond, O, S,

$$\begin{array}{c} \text{S} \\ \parallel \\ \text{O} \end{array}, \quad \begin{array}{c} \text{S} \\ \parallel \\ (\text{O})_2 \end{array}, \quad -\text{NH}-\begin{array}{c} \text{C} \\ \parallel \\ \text{O} \end{array}-, \quad -\underset{\text{alkyl}}{\text{N}}-\begin{array}{c} \text{C} \\ \parallel \\ \text{O} \end{array}-, \quad -\begin{array}{c} \text{C} \\ \parallel \\ \text{O} \end{array}- \quad \text{or} \quad -\underset{\text{OH}}{\text{C}}-\text{H}$$

with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond; R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that preferably

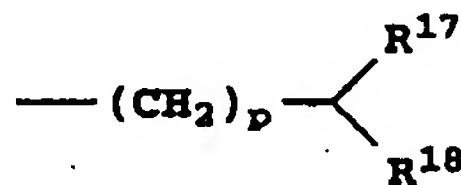
(1) when R¹² is H, aryloxy, alkoxy or arylalkoxy,
then Z² is $\text{—NH—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$, $\text{—}\underset{\text{alkyl}}{\text{N}}\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$, $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$ or a bond and

(2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; R¹³, R¹⁴, R¹⁵, and R¹⁶ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

R^{15a} and R^{16a} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy,

arylcarbonylamino, alkylcarbonylamino, arylalkyl,
heteroaryl, heteroarylalkyl, or aryloxy;
or R¹ is a group of the structure

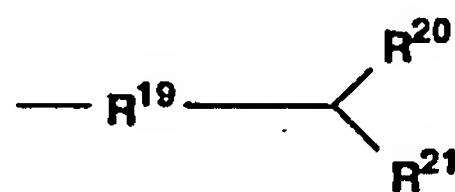


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wherein p is 1 to 8 and R¹⁷ and R¹⁸ are each independently
H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl,
heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one
of R¹⁷ and R¹⁸ being other than H;

10

or R¹ is a group of the structure



wherein R¹⁹ is aryl or heteroaryl;

R²⁰ is aryl or heteroaryl;

15

R²¹ is H, alkyl, aryl, alkylaryl, arylalkyl,
aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl,
heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or
cycloalkylalkoxy;

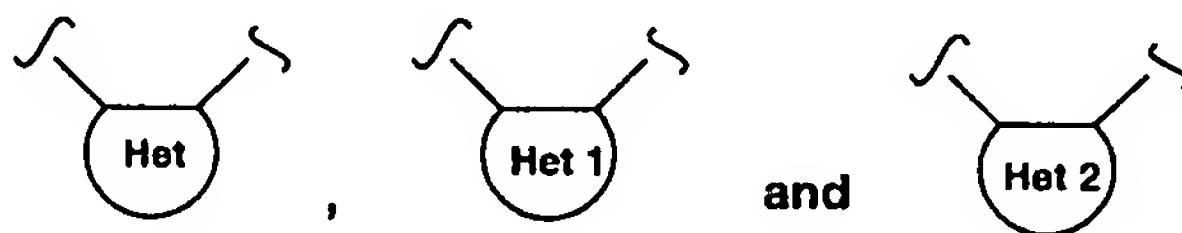
R², R³, R⁴ are independently hydrogen, halo, alkyl,
20 alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto,
arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl,
heteroarylalkyl, hydroxy or haloalkyl;

R⁵ is independently alkyl, alkenyl, alkynyl, aryl,
alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl,
25 heteroarylalkyl, cycloalkyl, cycloalkylalkyl,
polycycloalkyl, polycycloalkylalkyl, cycloalkenyl,
cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl,
polycycloalkenyl, polycycloalkenylalkyl,
heteroarylcarbonyl, amino, alkylamino, arylamino,
30 heteroarylamino, cycloalkyloxy, cycloalkylamino, all
optionally substituted through available carbon atoms with
1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl,
haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl,
cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cyclohetero-
35 alkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl,

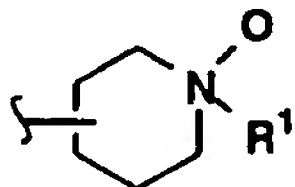
arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl,
 arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl,
 heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano,
 amino, substituted amino, thiol, alkylthio, arylthio,
 5 heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl,
 arylaminocarbonyl, alkoxy carbonyl, aminocarbonyl,
 alkynylaminocarbonyl, alkylaminocarbonyl,
 alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy,
 alkylcarbonylamino, arylcarbonylamino, arylsulfinyl,
 10 arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl,
 arylsulfonylamino, heteroarylcarbonylamino,
 heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl,
 alkylsulfinyl;

R^6 is hydrogen or C_1 - C_4 alkyl or C_1 - C_4 alkenyl; all
 15 optionally substituted with 1, 2, 3 or 4 groups which may
 independently be any of the substituents listed in the
 definition of R^5 set out above;

R^7 is alkyl, aryl or arylalkyl wherein alkyl by
 itself or as part of arylalkyl is optionally substituted
 20 with oxo $\left(\begin{smallmatrix} O \\ || \end{smallmatrix} \right)$;

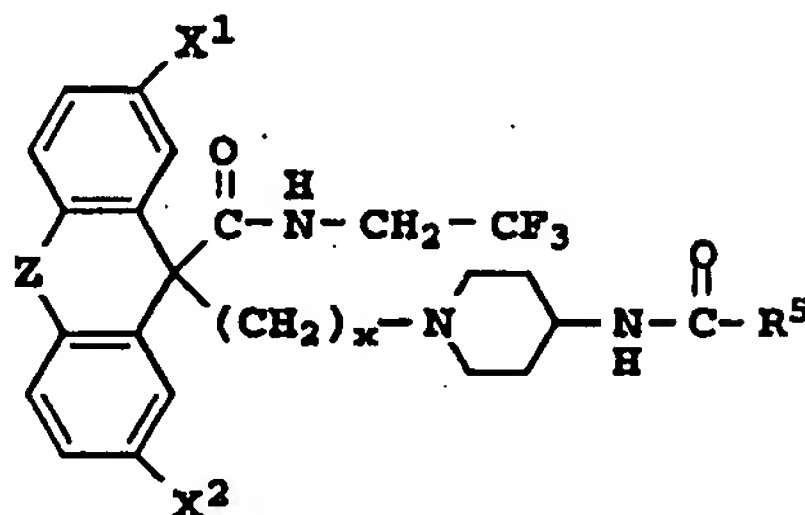


are the same or different and are independently selected
 from heteroaryl containing 5- or 6-ring members; and

25 N-oxides  thereof; and

pharmaceutically acceptable salts thereof; with
 the provisos that preferably where in the first formula X
 is CH_2 , and R^2 , R^3 and R^4 are each H, then R^1 will be other
 than 3,3-diphenylpropyl, and preferably in the fifth
 30 formula, where one of R^2 , R^3 and R^4 is 6-fluoro, and the
 others are H, R^7 will be other than 4-(2-methoxyphenyl).

The MTP inhibitors disclosed in U.S. application Serial No. 548,811 filed January 11, 1996 (file DC21h), have the structure



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including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;

x^1 and x^2 are independently selected from H or halo;

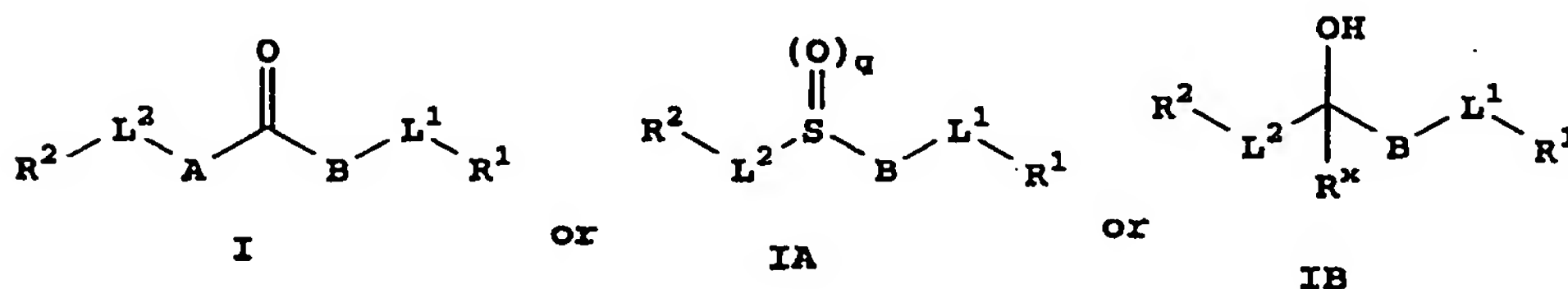
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x is an integer from 2 to 6;

R^5 is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each R^5 group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different.

15

The MTP inhibitors disclosed in U.S. provisional application No. 60/017,224, filed May 9, 1996 (file HX79a*) have the structure



20

including pharmaceutically acceptable salts thereof, wherein q is 0, 1 or 2;

A is (1) a bond;

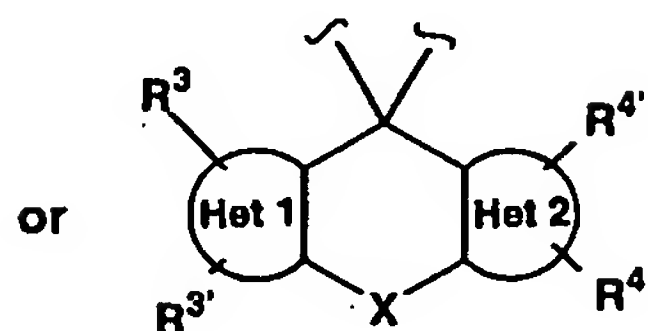
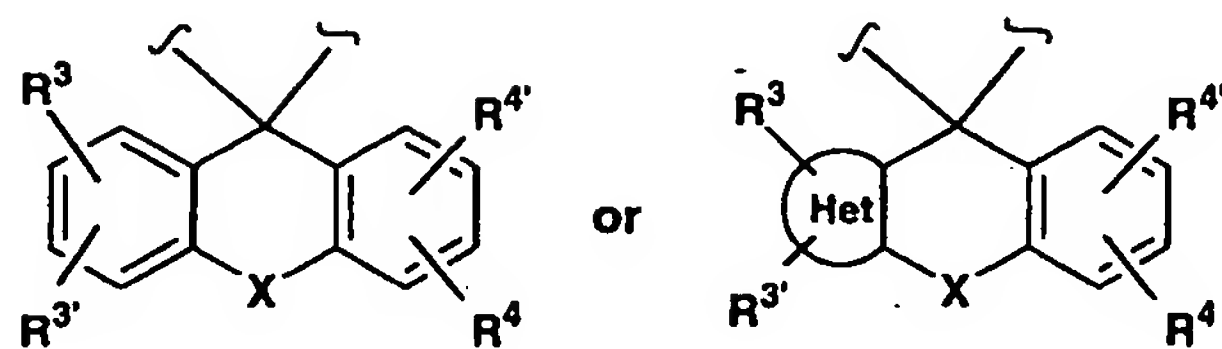
(2) -O- ; or

25



where R^5 is H or lower alkyl or R^5 together with R^2 forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring.

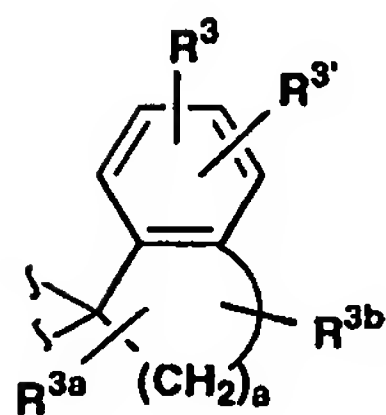
B is a fluorenyl-type group of the structure:



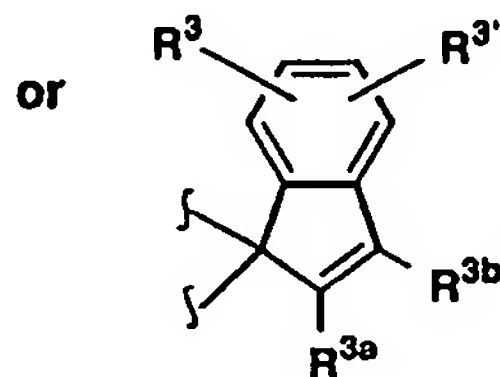
(the above B is also referred to as a fluorenyl-type ring or moiety); or

5

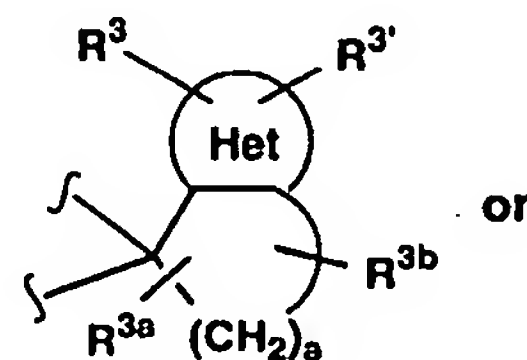
B is an indenyl-type group of the structure :



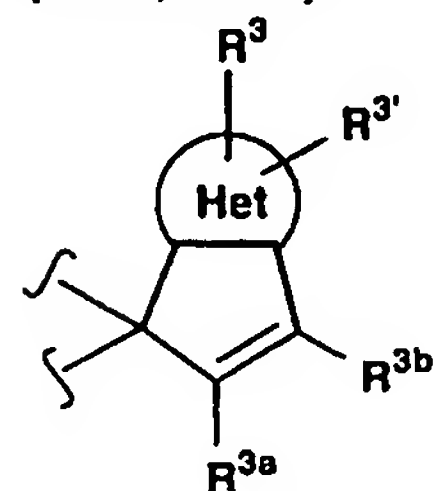
(a = 2,3 or 4)



or



or



(the above B is also referred to as an indenyl-type ring or moiety);

10

R^x is H, alkyl or aryl;

15

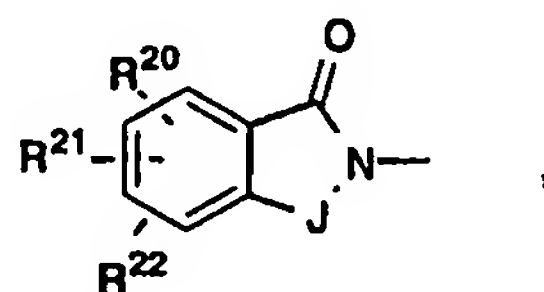
20

R¹ is alkyl, alkenyl, alkynyl, alkoxy, (alkyl or aryl)₃Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, heteroaryl, heteroaryl amino, heteroaryloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, -PO(R¹³)(R¹⁴), (where R¹³ and R¹⁴ are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy,

cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); R^1 can also be aminocarbonyl (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)₂alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring, such as 1,3-dioxane or 1,3-dioxolane, connected to L^1 (or L^2 in the case of R^2) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L^1 (or L^2 in the case of R^2) at the 4-position.

The R^1 group may have from one to four substituents, which can be any of the R^3 groups or R^1 groups, and any of the preferred R^1 substituents set out below.

R^1 may be substituted with the following preferred substituents: alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxy carbonylamino, uriedo (where the uriedo nitrogens may be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



25

where J is: CHR^{23} , $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}$, $\text{--}\underset{\text{R}^{24}}{\text{CH}}\text{--}\underset{\text{R}^{25}}{\text{CH}}\text{--}$ or $\text{--}\underset{\text{R}^{24}}{\text{C}}=\underset{\text{R}^{25}}{\text{C}}\text{--}$,

R^{23} , R^{24} and R^{25} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

30

R^{20} , R^{21} , R^{22} are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and

these preferred substituents may either be directly attached to R^1 , or attached via an alkylene chain at an open position.

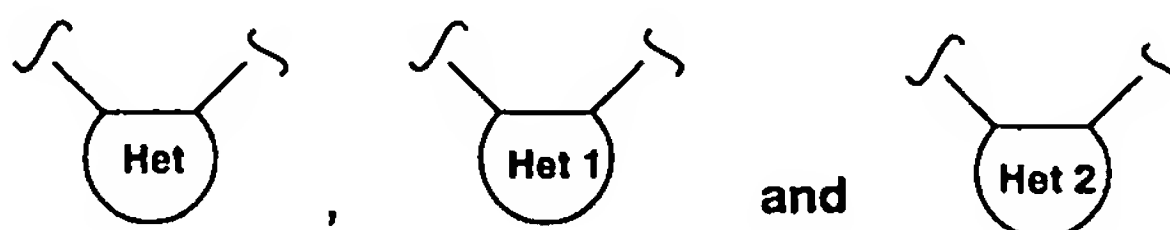
R^2 is the same or different from R^1 and is independently any of the groups set out for R^1 , H, polyhaloalkyl (such as CF_3CH_2 , $CF_3CF_2CH_2$ or CF_3) or cycloheteroalkyl, and may be substituted with one to four of any of the groups defined for R^3 , or any of the substituents preferred for R^1 .

L^1 is a linking group containing from 1 to 10 carbons in a linear chain (including alkylene, alkenylene or alkynylene), which may contain, within the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group optionally substituted with alkyl or aryl, an oxo group; and may be substituted with one to five alkyl or halo groups (preferably F).

L^2 may be the same or different from L^1 and may independently be any of the L^1 groups set out above or a single bond.

R^3 , $R^{3'}$, R^4 and $R^{4'}$ may be the same or different and are independently selected from H, halogen, CF_3 , haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

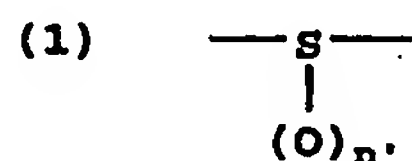
R^{3a} and R^{3b} are the same or different and are independently any of the R^3 groups except hydroxy, nitro, amino or thio;



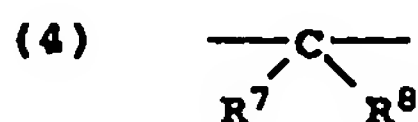
35

are the same or different and independently represent a 5 or 6 membered heteroaryl ring which may contain 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides.

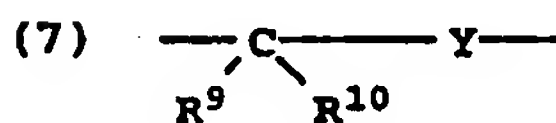
5 X (in the fluorenyl type ring) is a bond, or is one of the following groups:



10



15



20 wherein

Y is O, N-R⁶ or S;

n' is 0, 1 or 2;

R⁶ is H, lower alkyl, aryl, -C(O)-R¹¹ or -C(O)-O-R¹¹;

25

R⁷ and R⁸ are the same or different and are independently H, alkyl, aryl, halogen, -O-R¹², or

R⁷ and R⁸ together can be oxygen to form a ketone;

R⁹, R¹⁰, R^{9'} and R^{10'} are the same or different and are independently H, lower alkyl, aryl or -O-R¹¹;

30

R^{9''} and R^{10''} are the same or different and are independently H, lower alkyl, aryl, halogen or -O-R¹¹;

R¹¹ is alkyl or aryl;

R^{12} is H, alkyl or aryl.

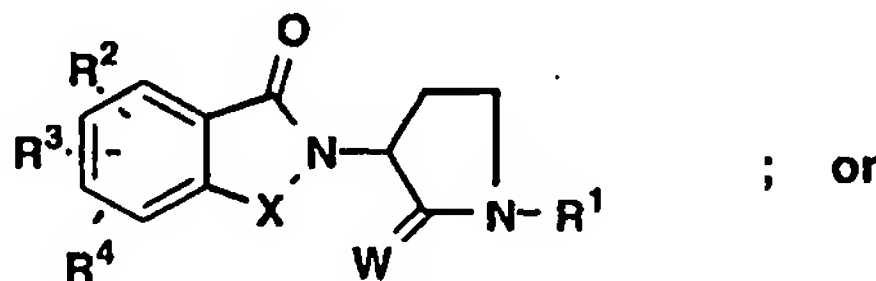
The following provisos apply to formula I preferred compounds:

- (a) when R^1 is unsubstituted alkyl or unsubstituted arylalkyl, L^1 cannot contain amino;
- (b) when R^1 is alkyl, L^1 cannot contain amino and oxo in adjacent positions (to form an amido group);
- (c) when R^2L^2A- is H_2N- , R^1L^1 cannot contain amino;
- (d) when R^1 is cyano, L^1 must have more than 2 carbons;
- (e) R^1L^1 must contain at least 3 carbons.

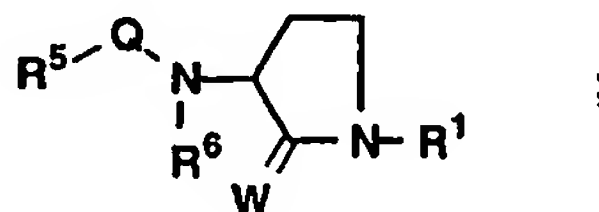
With respect to compounds IA and IB, R^2L^2 cannot have an O or N atom directly attached to $S(=O)_q$ or $CR^x(OH)$, and for IA, R^2L^2 cannot be H.

- 15 With respect to preferred compounds of formula IA and IB, where R^1 is cycloheteroalkyl, R^1 is exclusive of 1-piperidinyl, 1-pyrrolidinyl, 1-azetidinyll or 1-(2-oxo-pyrrolidinyl).

20 The MTP inhibitors disclosed in U.S. provisional application No. 60/017,253, filed May 10, 1996, (file HX82*) are pyrrolidine compounds and have the structure I



II



25

where Q is $-\overset{\text{O}}{\parallel}{\text{C}}-$ or $-\overset{\text{O}}{\parallel}{\text{S}}(\text{O})_2-$;

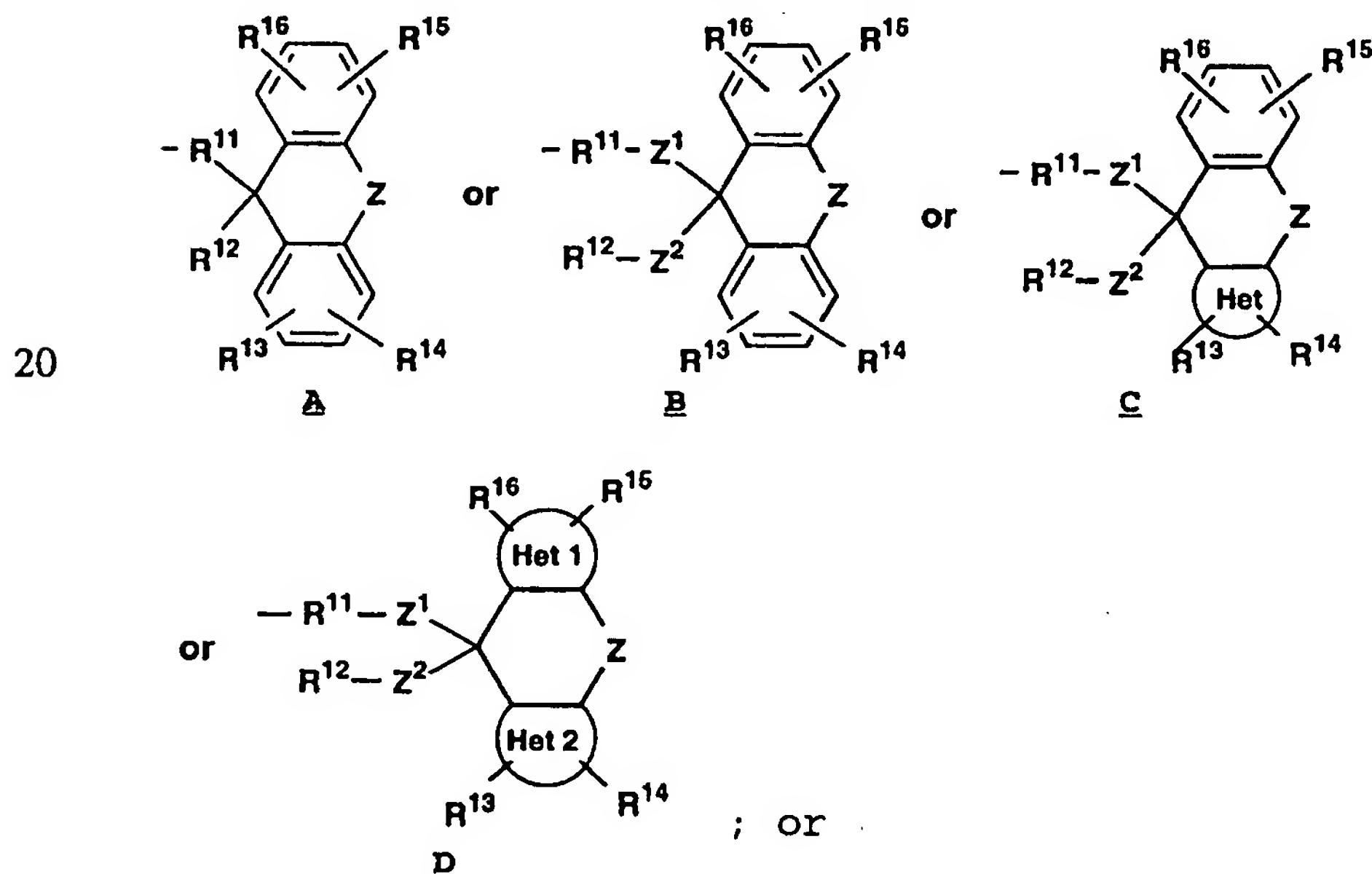
W is H, H or O;

30 X is: CHR^8 , $-\overset{\text{O}}{\parallel}{\text{C}}-$, $-\underset{\text{R}^9}{\text{CH}}-\underset{\text{R}^{10}}{\text{CH}}-$ or $-\underset{\text{R}^9}{\text{C}}=\underset{\text{R}^{10}}{\text{C}}-$;

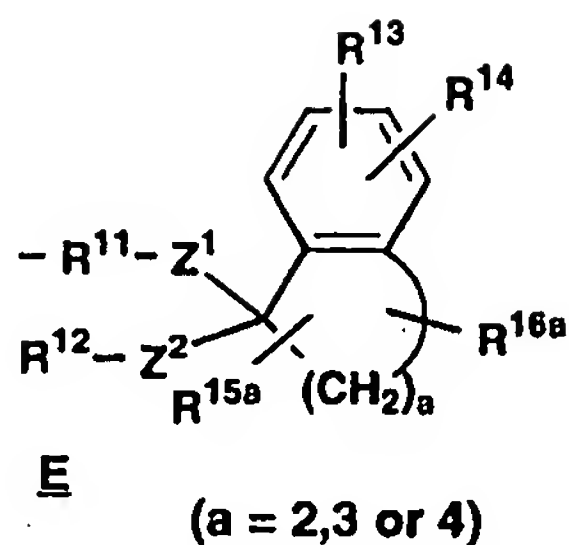
R^8 , R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons); all of the aforementioned R^1 groups being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo; or

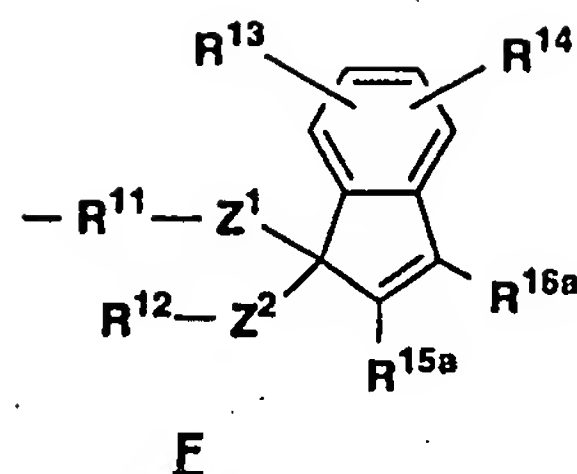
R^1 is a fluorenyl-type group of the structure



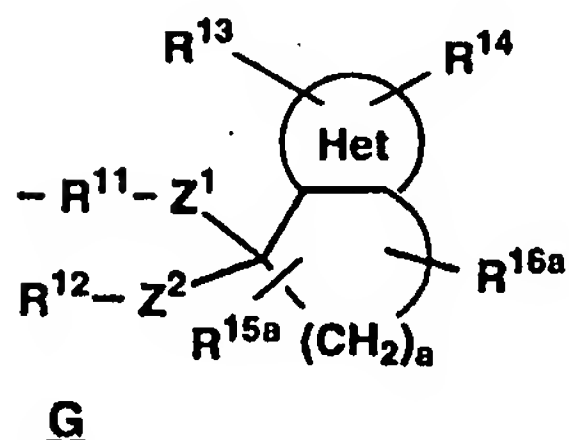
R^1 is an indenyl-type group of the structure



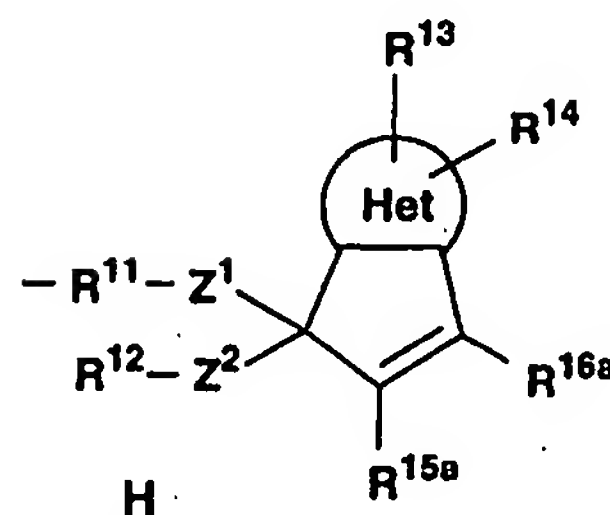
or



or

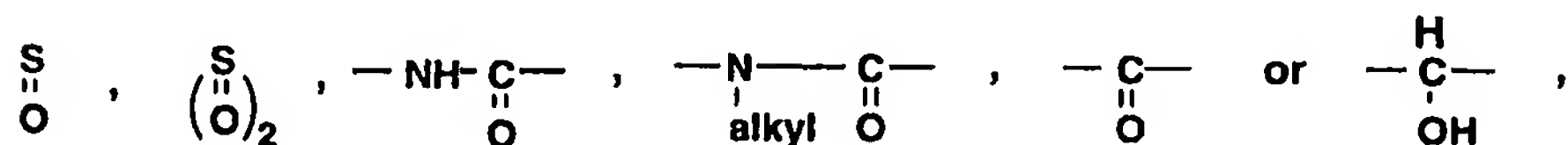


or



;

5 Z^1 and Z^2 are the same or different and are independently a bond, O, S,

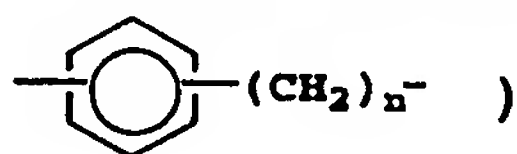


with the proviso that with respect to **B**, at least one of Z^1 and Z^2 will be other than a bond;

10 R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example



or mixed arylene-alkylene (for example



15 where n is 1 to 6;

R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the

20 provisos that (1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is

$$-\text{NH}-\text{C}(=\text{O})-, \quad -\text{N}(\text{alkyl})-\text{C}(=\text{O})-, \quad -\text{C}(=\text{O})- \quad \text{or a bond;}$$

and (2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

5 R^{13} , R^{14} , R^{15} , and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, 10 alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

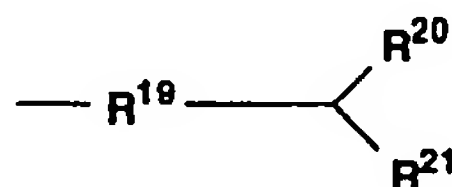
R^{15a} and R^{16a} are independently any of the R^{15} or R^{16} groups except hydroxy, nitro, amino or thio;

or R^1 is



wherein p is 1 to 8 and R^{17} and R^{18} are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of R^{17} and R^{18} being other than H;

20 or R^1 is



wherein R^{19} is aryl or heteroaryl;

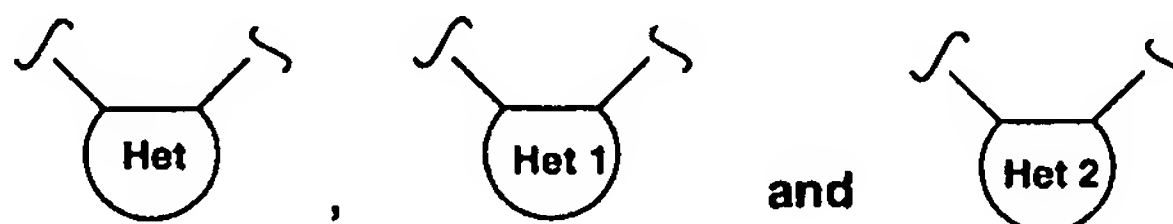
R^{20} is aryl or heteroaryl;

25 R^{21} is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

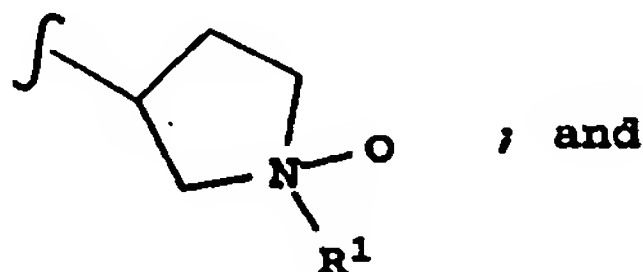
30 R^2 , R^3 , R^4 are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R^5 is alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloheteroalkyl,

- heteroaryloxy, cycloalkylalkyl, polycycloalkyl,
 polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl,
 polycycloalkenyl, polycycloalkenylalkyl,
 heteroarylcarbonyl, amino, alkylamino, arylamino,
 5 heteroarylamino, cycloalkyloxy, cycloalkylamino, all of the
 R^5 substituents and R^6 substituents (set out hereinafter)
 being optionally substituted through available carbon atoms
 with 1, 2, 3 or 4 groups selected from hydrogen, halo,
 alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl,
 10 cycloalkyl, cycloalkylalkyl, cycloheteroalkyl,
 cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl,
 arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy,
 aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo,
 heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy,
 15 nitro, cyano, amino, substituted amino (wherein the amino
 includes 1 or 2 substituents which are alkyl, aryl or
 heteroaryl, or any of the other aryl compounds mentioned in
 the definitions), thiol, alkylthio, arylthio,
 heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl,
 20 arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl,
 alkynylaminocarbonyl, alkylaminocarbonyl,
 alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy,
 alkylcarbonylamino, arylcarbonylamino, arylsulfinyl,
 arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl,
 25 arylsulfonylamino, heteroarylcarbonylamino,
 heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or
 alkylsulfinyl. Where R^5 is phenyl, aryl, heteroaryl or
 cycloalkyl; this group preferably includes an ortho
 hydrophobic substituent such as alkyl, haloalkyl (with up
 30 to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo
 groups), aryl, aryloxy or arylalkyl;
 R^6 is hydrogen or C_1 - C_4 alkyl or C_1 - C_4 alkenyl;



are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and including N-oxides of the formulae I and II compounds, that is

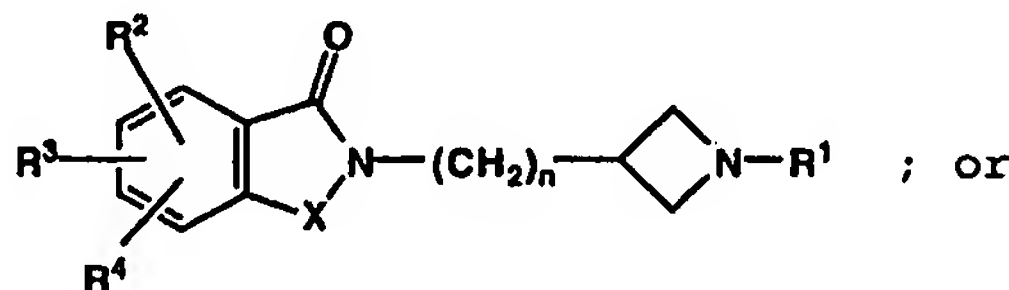


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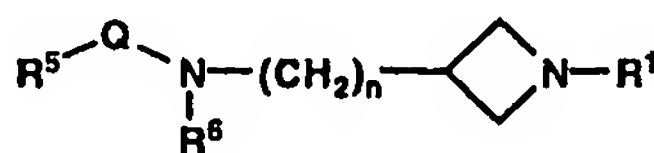
including pharmaceutically acceptable salts thereof.

The MTP inhibitors disclosed in U.S. provisional application No. 60/017,254, filed May 10, 1996, (file HX84*) are azetidine compounds which have the structure

10 I



II



where Q is $\text{--}\overset{\text{O}}{\parallel}\text{C--}$ or $\text{--}\overset{\text{O}}{\parallel}\text{S}\overset{\text{O}}{\parallel}\text{--}$;

15

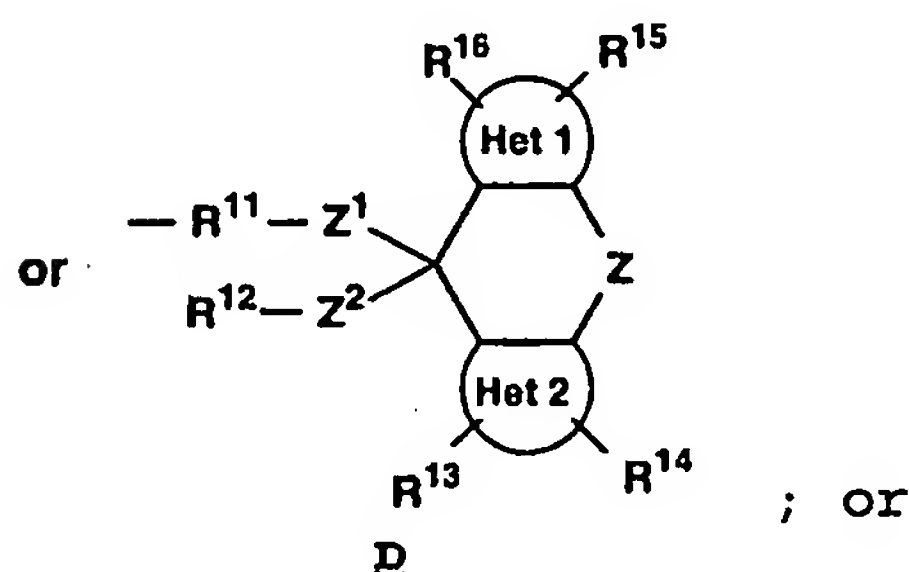
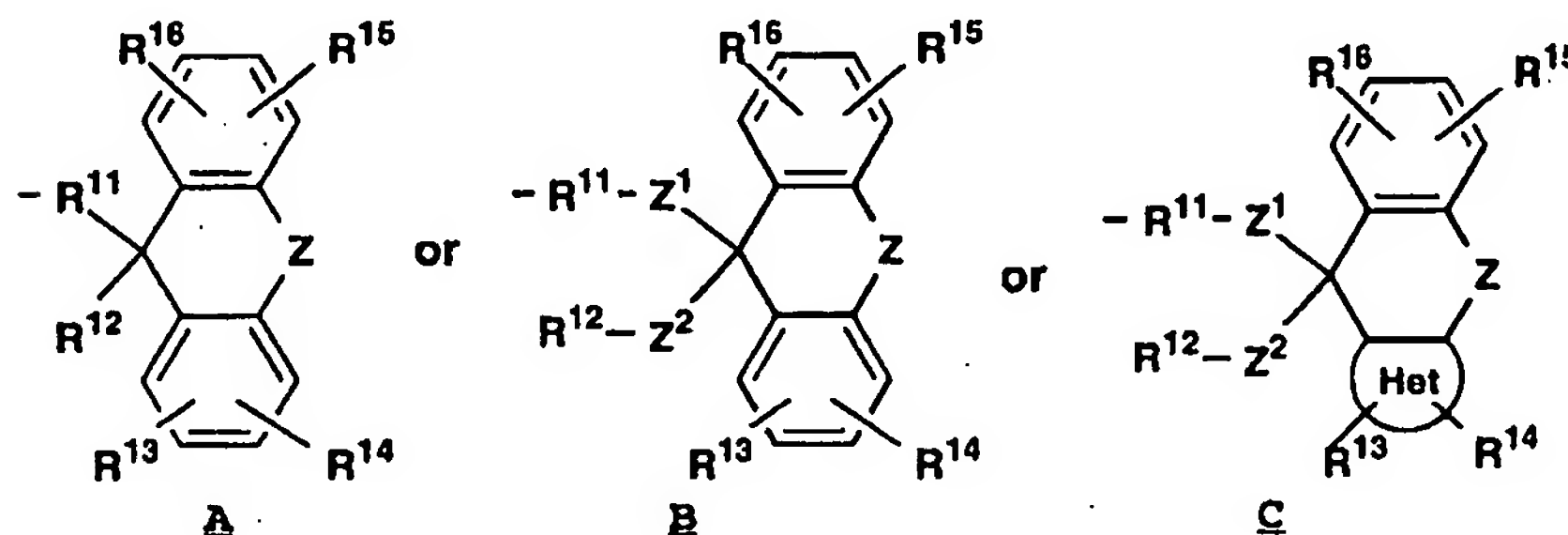
X is: CHR^8 , $\text{--}\overset{\text{O}}{\parallel}\text{C--}$, $\text{--}\underset{\text{R}^9}{\text{CH}}\text{--}\underset{\text{R}^{10}}{\text{CH}}\text{--}$ or $\text{--}\underset{\text{R}^9}{\text{C}}=\underset{\text{R}^{10}}{\text{C}}\text{--}$;
n is 0 or 1;

R^8 , R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

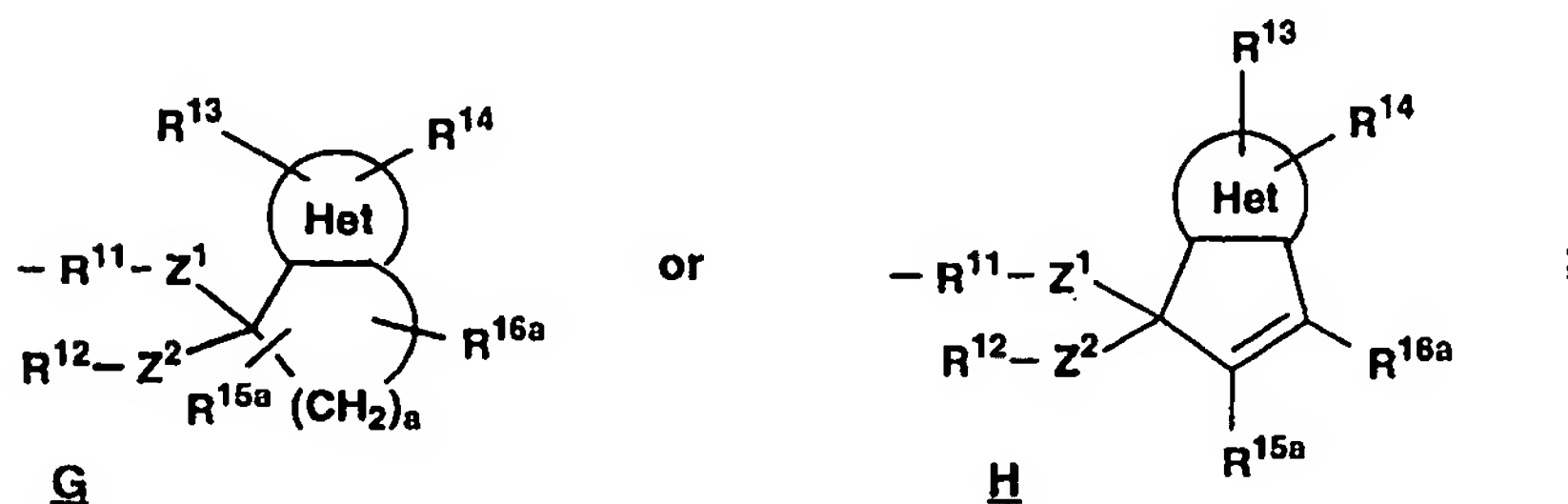
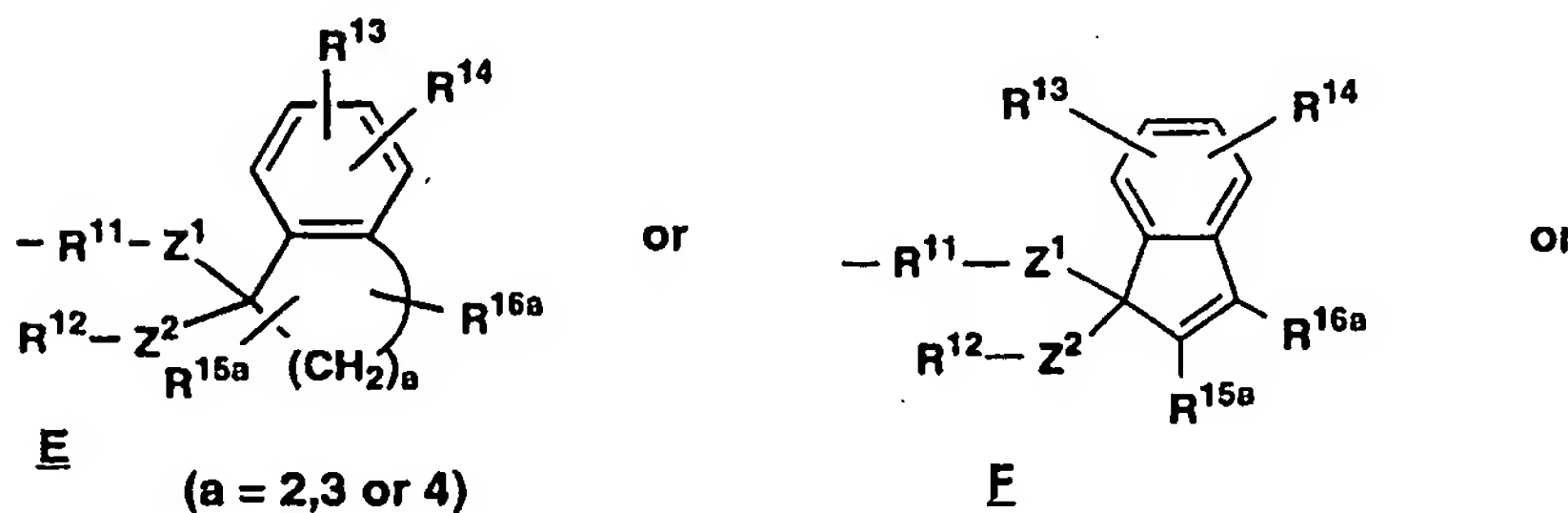
R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons); all of the aforementioned R^1 groups being

optionally substituted through available carbon atoms with
 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl,
 alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto,
 arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl,
 5 fluorenyl, heteroarylalkyl, hydroxy or oxo; or

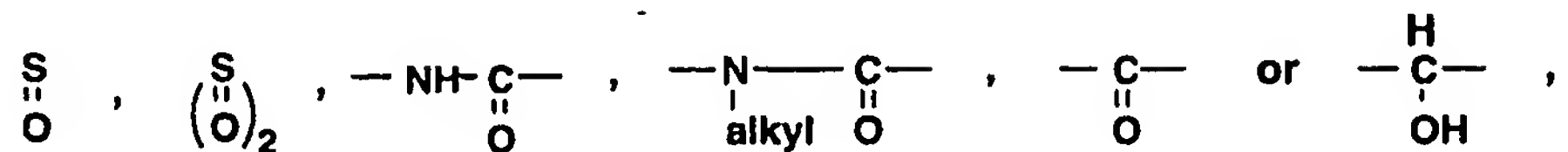
R^1 is a fluorenyl-type group of the structure



R^1 is an indenyl-type group of the structure



Z^1 and Z^2 are the same or different and are independently a bond, O, S,

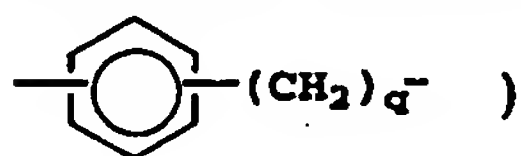


5 with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond;

R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example



10 or mixed arylene-alkylene (for example



where q is 1 to 6;

R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl,

15 heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the provisos that (1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is $-\text{NH}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$, $\begin{array}{c} \text{N} \\ | \\ \text{alkyl} \end{array}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$, $-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-$ or a bond;

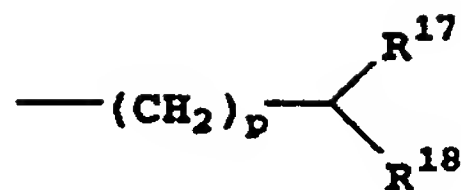
20 and (2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

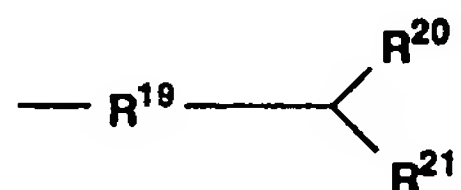
25 R^{13} , R^{14} , R^{15} , and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, 30 or aryloxy;

R^{15a} and R^{16a} are independently any of the R^{15} or R^{16} groups except hydroxy, nitro, amino or thio;

or R^1 is



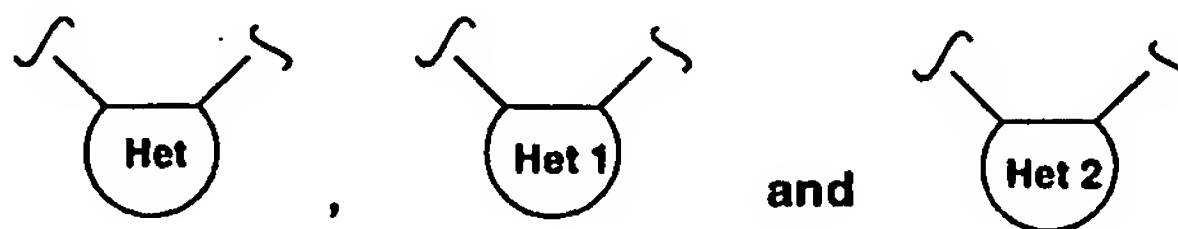
wherein p is 1 to 8 and R¹⁷ and R¹⁸ are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least
 5 one of R¹⁷ and R¹⁸ being other than H;
 or R¹ is



wherein R¹⁹ is aryl or heteroaryl;
 R²⁰ is aryl or heteroaryl;
 10 R²¹ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;
 R², R³, R⁴ are independently hydrogen, halo, alkyl,
 15 alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;
 R⁵ is alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, hetero-
 20 arylalkyl, cycloalkyl, cycloheteroalkyl, heteroaryloxy, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy,
 25 cycloalkylamino, all of the R⁵ substituents and R⁶ substituents (set out hereinafter) being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl,
 30 aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted

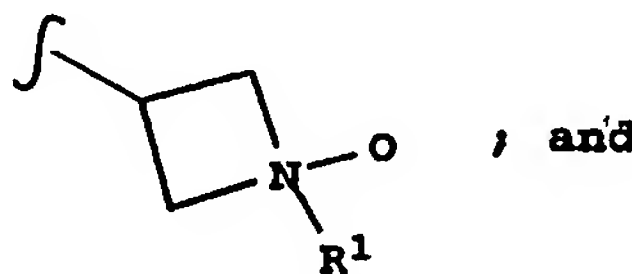
amino (wherein the amino includes 1 or 2 substituents which are alkyl, aryl or heteroaryl, or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylsulfonyl, or alkylsulfinyl. Where R^5 is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups), aryl, aryloxy or arylalkyl;

R^6 is hydrogen or C_1 - C_4 alkyl or C_1 - C_4 alkenyl;



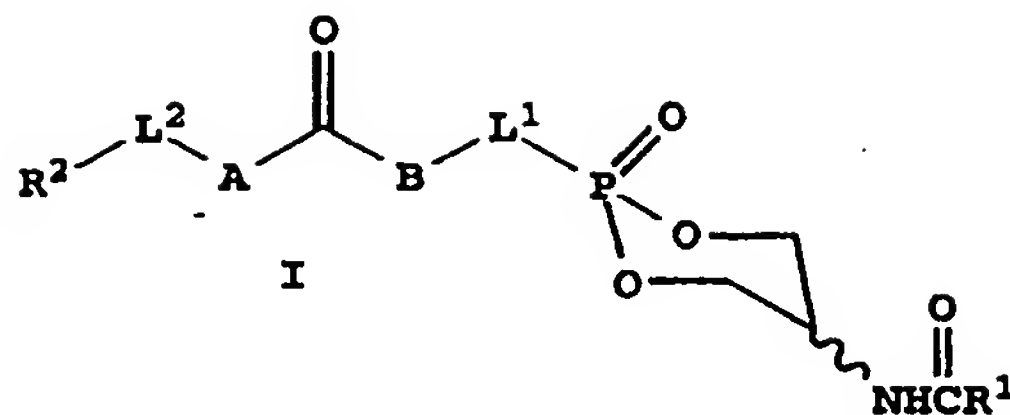
are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

including N-oxides of the formulae I and II compounds, that is



including pharmaceutically acceptable salts thereof.

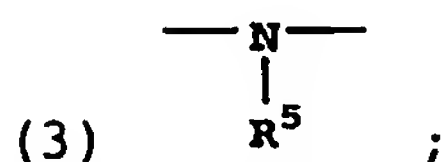
The MTP inhibitors disclosed in U.S. provisional application No. 60/028,216, filed October 1, 1996, have the structure



including pharmaceutically acceptable salts thereof,
wherein

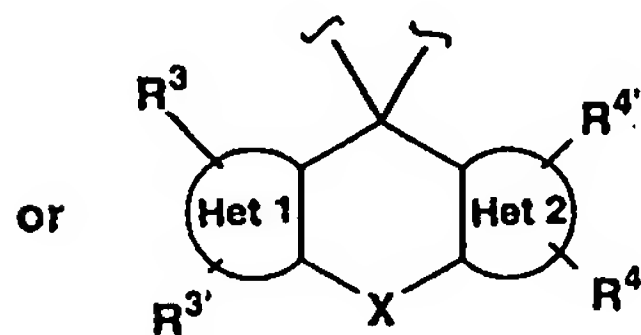
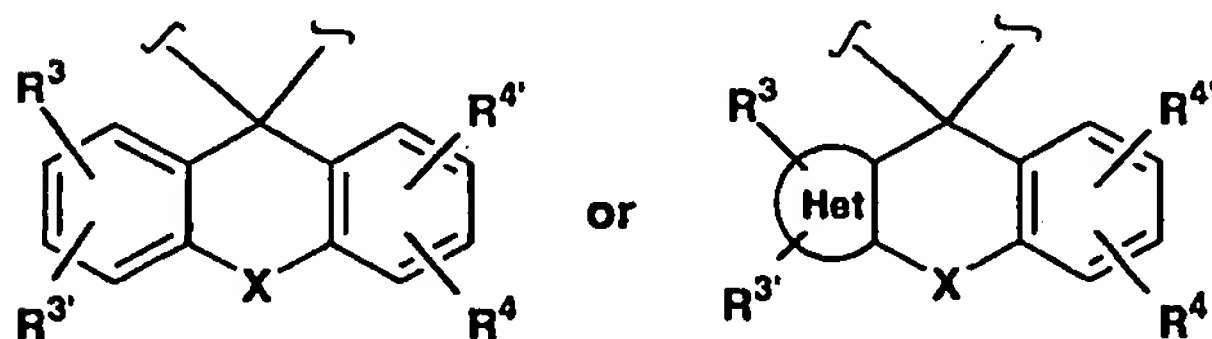
A is (1) a bond;

5 (2) -O- ; or



where R⁵ is H or lower alkyl or R⁵ together with R² forms a
carbocyclic or heterocyclic ring system containing 4 to 8
10 members in the ring.

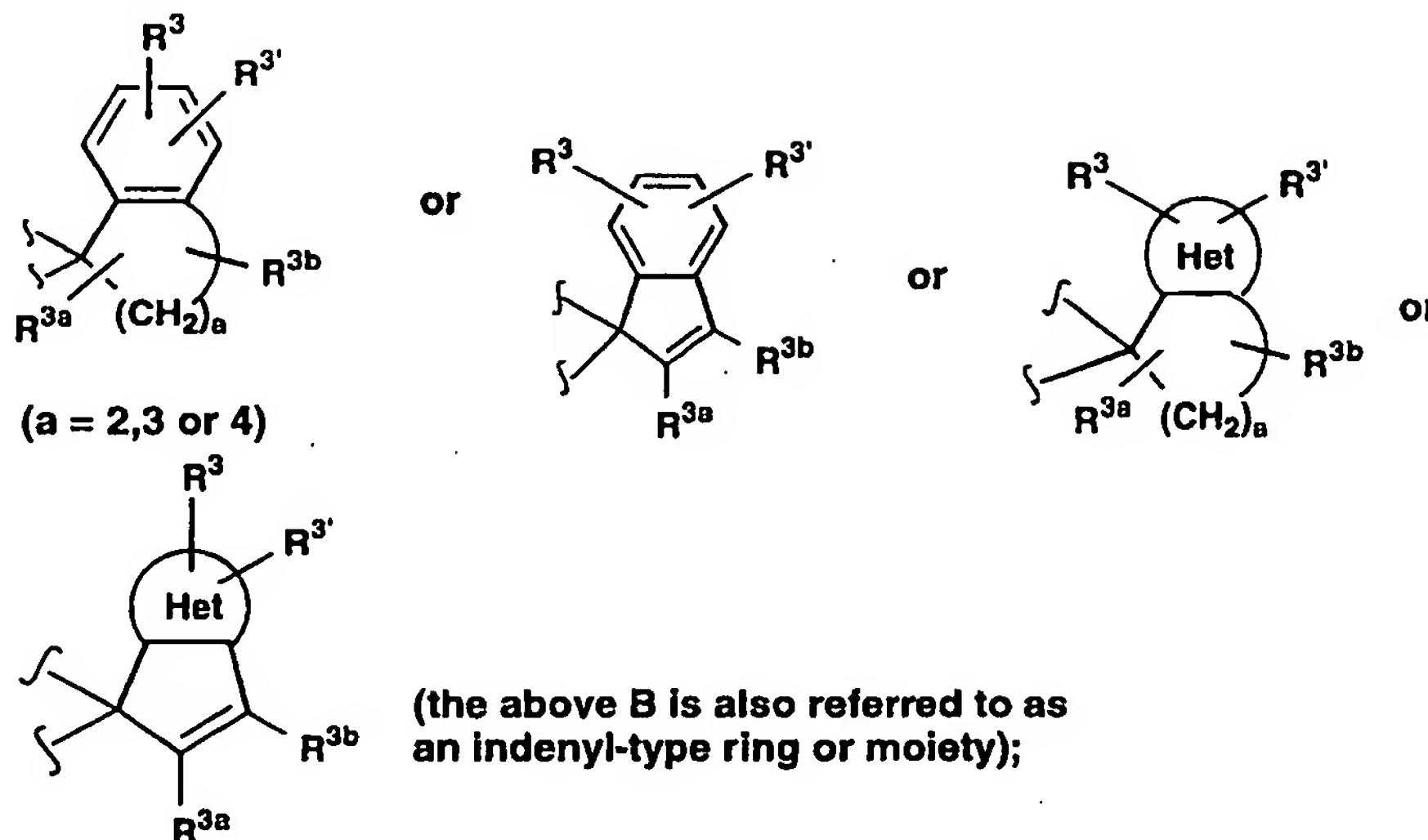
B is a fluorenyl-type group of the structure:



(the above B is also referred to as a
fluorenyl-type ring or moiety); or

15

B is an indenyl-type group of the structure



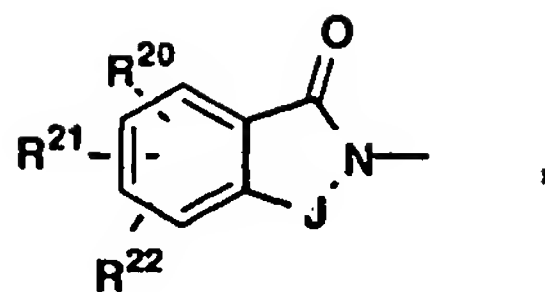
- R^1 is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cyclohetero-alkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino,

heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

R^2 is alkyl, alkenyl, alkynyl, alkoxy, (alkyl or aryl)₃Si (where each alkyl or aryl group is independent),
5 cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, heteroaryl, heteroarylamino, heteroaryloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl,
10 alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, -PO(R^{13})(R^{14}), (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); R^1 can also be aminocarbonyl
15 (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxy or aryloxy)₂alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to
20 form a ring, such as 1,3-dioxane or 1,3-dioxolane, connected to L^1 (or L^2 in the case of R^2) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L^1 (or L^2 in the case of R^2) at the 4-position.

The R^2 group may have from one to four substituents,
25 which can be any of the R^3 groups or R^2 groups, and any of the preferred R^2 substituents set out below.

R^2 may be substituted with the following preferred substituents: alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino,
30 alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, uriedo (where the uriedo nitrogens may be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a
35 nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



where J is: CHR^{23} , $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$, $\text{—}\underset{\text{R}^{24}}{\text{CH}}\text{—}\underset{\text{R}^{25}}{\text{CH}}\text{—}$ or $\text{—}\overset{\text{R}^{24}}{\text{C}}=\overset{\text{R}^{25}}{\text{C}}\text{—}$;

R^{23} , R^{24} and R^{25} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

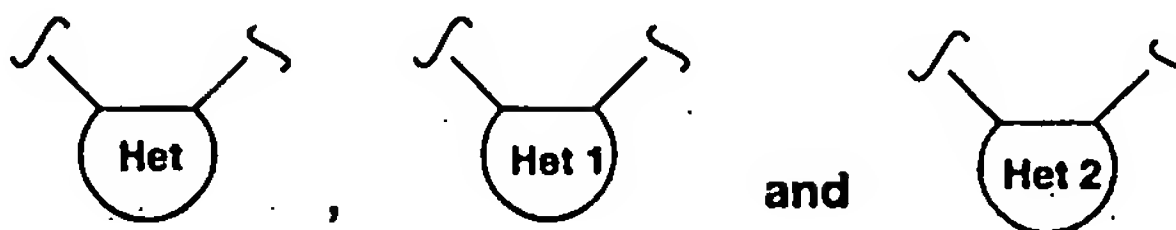
R^{20} , R^{21} , R^{22} are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these preferred substituents may either be directly attached to R^1 , or attached via an alkylene chain at an open position.

L^1 is a linking group containing from 1 to 10 carbons in a linear chain (including alkylene, alkenylene or alkynylene), which may contain, within the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group optionally substituted with alkyl or aryl, an oxo group; and may be substituted with one to five alkyl or halo groups (preferably F).

L^2 may be the same or different from L^1 and may independently be any of the L^1 groups set out above or a single bond.

R^3 , $\text{R}^{3'}$, R^4 and $\text{R}^{4'}$ may be the same or different and are independently selected from H, halogen, CF_3 , haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

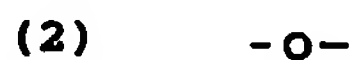
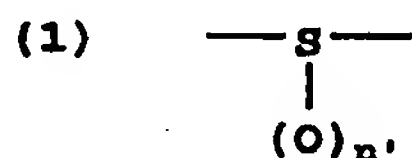
R^{3a} and R^{3b} are the same or different and are independently any of the R^3 groups except hydroxy, nitro, amino or thio;



5

are the same or different and independently represent a 5 or 6 membered heteroaryl ring which may contain 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides.

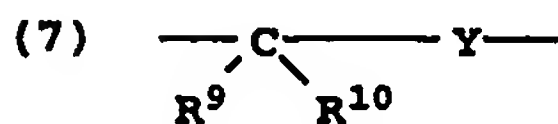
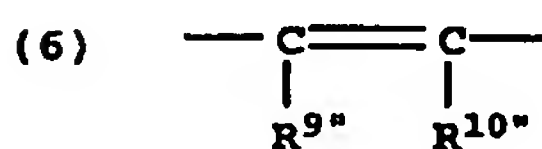
10 X (in the fluorenyl type ring) is a bond, or is one of the following groups:



15



20



25 wherein

Y is O, N- R^6 or S;

n' is 0, 1 or 2;

R^6 is H, lower alkyl, aryl, $-\text{C}(\text{O})-\text{R}^{11}$ or $-\text{C}(\text{O})-\text{O}-\text{R}^{11}$;

30

R^7 and R^8 are the same or different and are independently H, alkyl, aryl, halogen, $-\text{O}-\text{R}^{12}$, or

R^7 and R^8 together can be oxygen to form a ketone;
 R^9 , R^{10} , $R^{9'}$ and $R^{10'}$ are the same or different and
 are independently H, -lower alkyl, aryl or $-O-R^{11}$;

$R^{9''}$ and $R^{10''}$ are the same or different and are
 5 independently H, lower alkyl, aryl, halogen or
 $-O-R^{11}$;

R^{11} is alkyl or aryl;

R^{12} is H, alkyl or aryl.

Compounds disclosed as preferred in each of the
 10 above applications are preferred for use in the present
 invention.

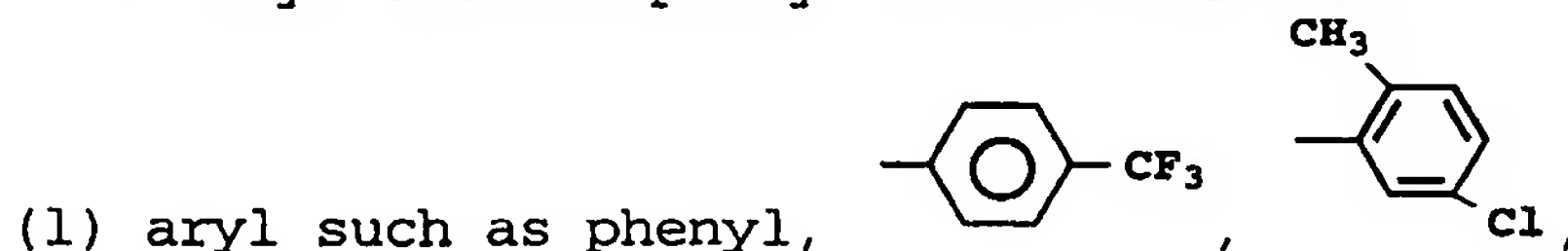
Most preferred MTP inhibitors to be employed in
 accordance with the present invention include preferred MTP
 inhibitors as set out in U.S. patent application Serial No.
 15 548,811, filed January 11, 1996 (file DC21h) and in U.S.
 provisional application No. 60/017,224, filed May 9, 1996
 (file HX79a*).

Thus, preferred compounds in U.S. patent application
 Serial No. 548,811 (file DC21h) for use herein are
 20 compounds

where Z is a bond;

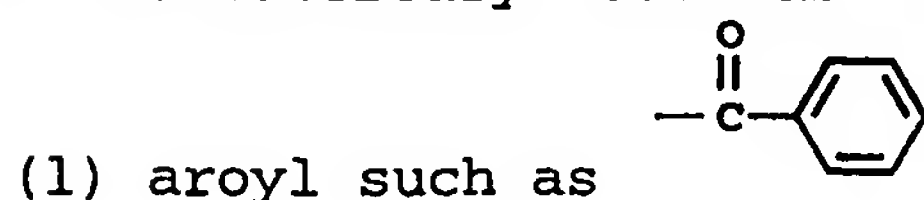
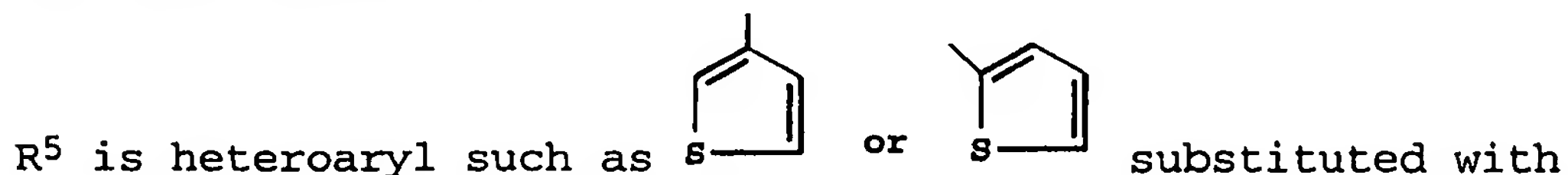
X^1 and X^2 are H;

R^5 is aryl such as phenyl substituted with



25 (2) heteroaryl such as

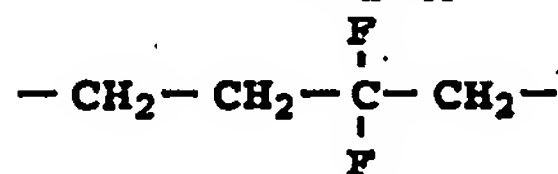
(3) halo such as Cl





(2) arylthio such as
wherein the R⁵ substituent is preferably in the position
adjacent to the carbon linked to $\overset{\text{O}}{\parallel}{\text{C}}$.

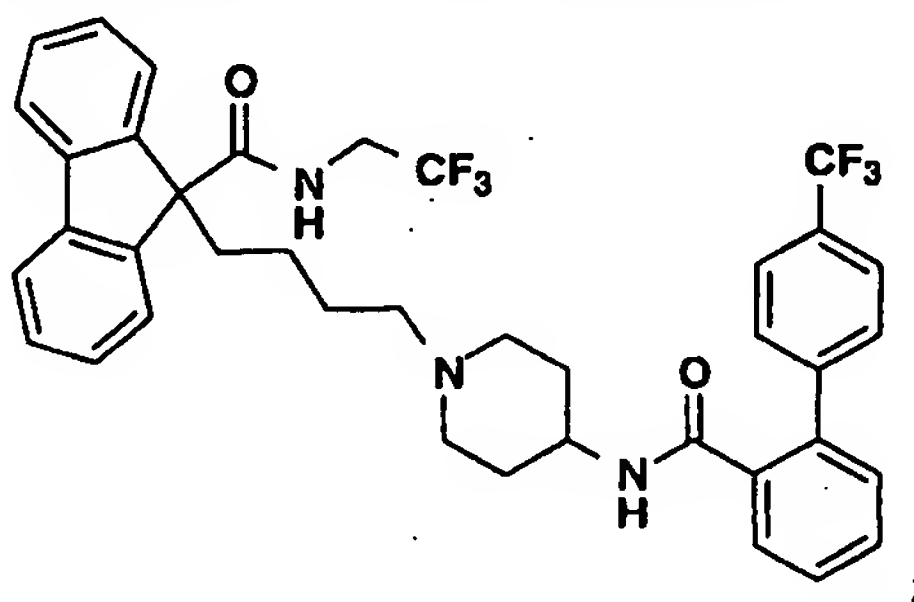
(CH₂)_x is -(CH₂)₄- or



5

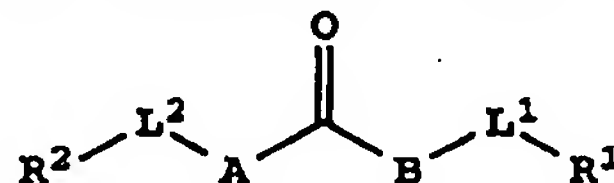
Most preferred is

9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidiny]butyl]-
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



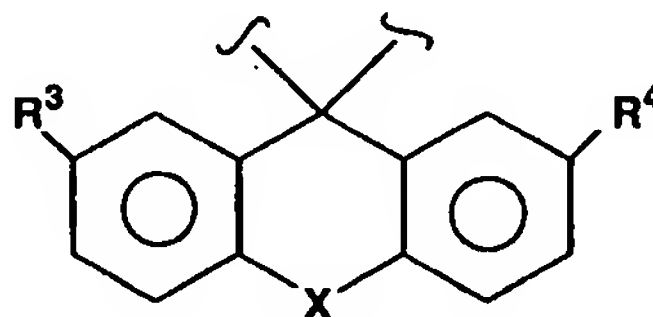
10

Preferred compounds in U.S. provisional application
No. 60/017,224 (file HX79a*) for use herein are MTP
inhibitor compounds of formula I that is



15 wherein A is NH,

B is



X is a bond, oxygen or sulfur; R³ and R⁴ are
independently H or F.

20

Preferred R¹ groups are aryl, preferably phenyl,
heteroaryl, preferably imidazolyl or pyridyl (preferably
substituted with one of the preferred R¹ substituents:
arylcarbonylamino, heteroarylcarbonylamino,

cycloalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl-sulfonylamino), PO(OAlkyl)₂, heteroarylthio, benzthiazole-2-thio, imidazole-2-thio, alkyl, or alkenyl, cycloalkyl
5 such as cyclohexyl, or 1,3-dioxan-2-yl.

Preferred R² groups are alkyl, polyfluoroalkyl (such as 1,1,1-trifluoroethyl), alkenyl, aryl or heteroaryl (preferably substituted with one of the preferred R¹ substituents above), or PO(OAlkyl)₂.

10 If R² is alkyl, 1,1,1-trifluoroethyl, or alkenyl, it is preferred that R¹ is other than alkyl or alkenyl.

It is preferred that L¹ contains 1 to 5 atoms in the linear chain and L² is a bond or lower alkylene.

Preferred embodiments of formula IA and formula IB
15 compounds of the invention include those where B, L¹, L², R¹ and R² are as set out with respect to the preferred embodiments of the formula I compounds, q is 0 or 2 and R^x is H.

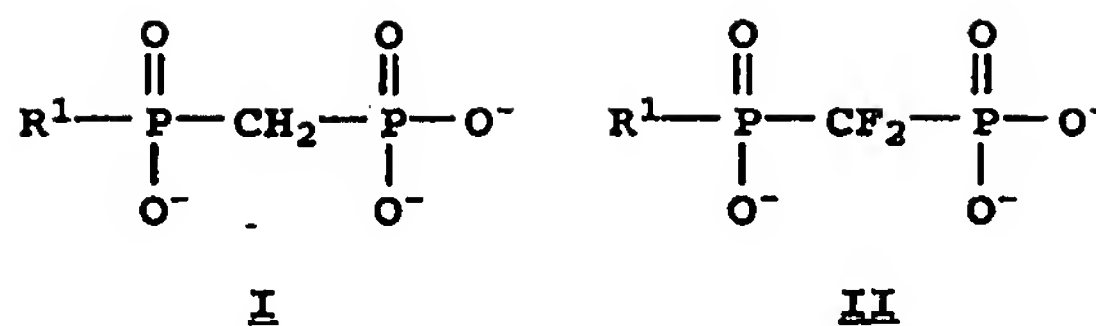
The other cholesterol lowering drugs or delipidating
20 drugs which may be used in the method of the invention include HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, probucol, niacin, niacin derivatives and the like.

25 The HMG CoA reductase inhibitors suitable for use herein include, but are not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and
30 related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171, with pravastatin, lovastatin or simvastatin being preferred. Other HMG CoA reductase inhibitors which may be employed
35 herein include, but are not limited to, fluvastatin, cerivastatin, atorvastatin, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No.

4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's
5 SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-di-substituted pyrrole,
10 furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as
15 disclosed in European Patent Application No. 0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

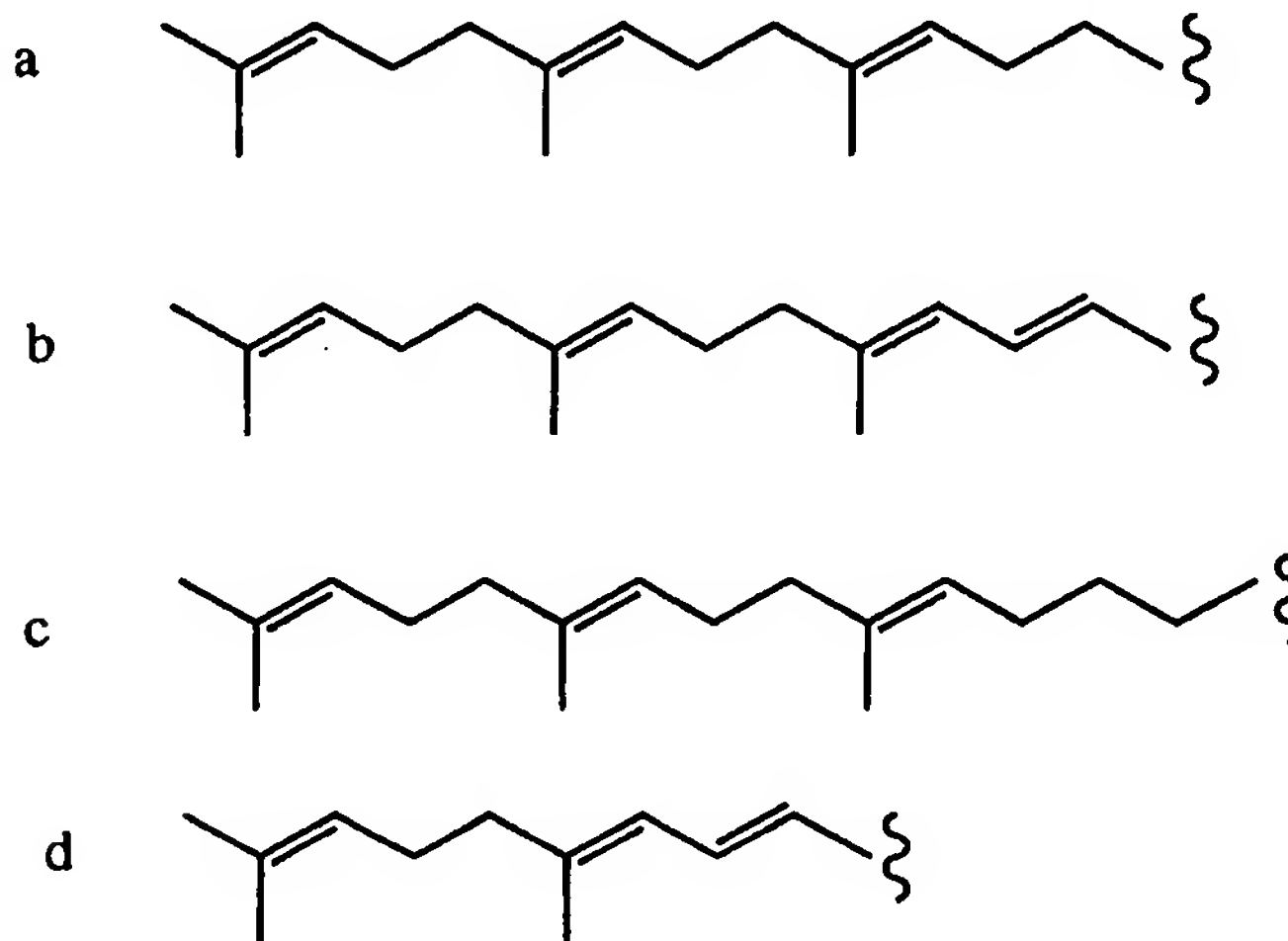
In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

20 The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α -phosphonosulfonates disclosed in U.S. application Serial No. 08/266,888, filed July 5, 1994 (HX59b), those disclosed by Biller et al, J. Med. Chem. 1988, Vol. 31, No. 10, pp 1869-
25 1871, including isoprenoid (phosphinylmethyl)phosphonates such as those of the formula



R¹

5



including the triacids thereof, triesters thereof and tripotassium and trisodium salts thereof as well as other squalene synthetase inhibitors disclosed in U.S. Patent Nos. 4,871,721 and 4,924,024 and in Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869 to 1871.

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem.; 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc. 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U. of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary.

Preferred are pravastatin, lovastatin or simvastatin.

All of the above U.S. applications are incorporated herein by reference.

5 Other cholesterol lowering drugs suitable for use herein include, but are not limited to, antihyperlipoproteinemic agents such as fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, 10 probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex[®], Polidexide[®]), as well as clofibrate, lipostabil (Rhone-Poulenc), Eisai E-5050 (an N- 15 substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 20 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as 25 disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

The above-mentioned U.S. patents are incorporated herein by reference.

30 The MTP inhibitor will be employed in a weight ratio to the other cholesterol lowering or delipidating agent (where present), in accordance with the present invention, within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

35 In carrying out the method of the present invention, the MTP inhibitor alone or optionally in combination with the other cholesterol lowering drug may be administered to mammalian species, such as monkeys, dogs, cats, rats,

humans, etc., and as such may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The dosages and formulations for the MTP inhibitor will be as disclosed in the various patents and applications discussed above.

The dosages and formulations for the other delipidating agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 75 mg/kg, one to four times daily.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

For parenteral administration, the MTP inhibitor will be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 8 mg/kg, one to four times daily.

The other cholesterol lowering or delipidating agent will be employed in amounts set out in the latest edition of the Physician's Desk Reference (PDR).

For oral administration, a satisfactory result may
5 be obtained employing an HMG CoA reductase inhibitor in dosages employed, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and
10 preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

15 A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount of from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

20 A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The serum cholesterol lowering drugs when present
25 will be employed in dosages normally employed as indicated in the Physician's Desk Reference, for each of such agents such as in an amount within the range of from about 2 mg to about 7500 mg and preferably from about 2 mg to about 4000 mg.

30 A preferred oral dosage form, such as tablets or capsules, will contain MTP inhibitor in an amount of from about 10 to about 400 mg, and the HMG CoA reductase inhibitor (where present) in an amount of from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and
35 more preferably from about 10 to about 50 mg.

The MTP inhibitor and other cholesterol lowering drug may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

5 The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

10 Tablets of various sizes can be prepared, e.g., of about 2 to 2000 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be
15 scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for
20 pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more
25 finely regulate the dosage schedule, the active substances may be administered separately in individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by
30 the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of MTP inhibitor and other
35 cholesterol lowering drug are more convenient and are preferred, especially in tablet or capsule form for oral administration.

In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Some of the active substances described above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The formulations as described above will be administered for a prolonged period, that is, for as long as the acid lipase deficiency exists. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed.

The following Examples represent preferred embodiments of the present invention.

Examples 1 and 2

5 Formulations suitable for oral administration are prepared as described below.

Capsules containing 1 mg MTP inhibitor BMS 201,038 (Example 1) and capsules containing 50 mg BMS 201,038 (Example 2) are produced from the following ingredients.

10

| <u>Ingredient</u> | <u>Example 1 Amount (mg/ Capsule)</u> | <u>Example 2 Amount (mg/ Capsule)</u> |
|-------------------------------------|---|---|
| BMS-201038 (1) | 1.1 | 56.9 |
| Lactose, Hydrous, NF ca. | 30.2 ca. | 99.9 |
| Lactose, Anhydrous, NF | 47.3 | 0.0 |
| Microcrystalline Cellulose, NF | 10.0 | 50.0 |
| Pregelatinized Starch, NF | 5.0 | 25.0 |
| Sodium Starch Glycolate, NF | 5.0 | 12.5 |
| Colloidal Silicon Dioxide, NF | 1.0 | 5.0 |
| Magnesium Stearate, NF | 0.3 | 0.6 |
| Purified Water, USP or | q.s. | q.s. |
| Water for Injection, USP | q.s. | q.s. |
| Gray, Opaque, Size #0 Capsule Shell | One Capsule | One Capsule |
| | about | about |
| Total Fill Weight | 100.0 | 250.0 |

15 (1) In Example 1 this amount is expressed in terms of the amount of methane sulfonic acid salt per capsule at 100% potency. In Example 2, this amount is expressed in terms of the free base. This is equivalent to 1 mg and 50 mg (Examples 1 and 2, respectively) of the free base.

20

The MTP inhibitor BMS 201,038, and colloidal silicon dioxide are blended in a suitable blender with lactose hydrous, microcrystalline cellulose, pregelatinized starch and a portion of sodium starch glycolate. The resulting
5 blend is wet granulated with water. The wet granulation is dried in a suitable dryer. The remaining portion of sodium starch glycolate is added to the granulation and mixed therein. Magnesium stearate is added to the granulation and mixed therein. The resulting blend is filled into
10 capsules.

Example 3

Pravastatin tablets (10, 20 or 40 mg as described in the 1996 PDR) and MTP inhibitor (BMS 201,238) tablets may
15 be administered as a combination in accordance with the teachings of the present invention. In addition, the pravastatin and MTP inhibitor tablets may be ground up into powders and used together in a single capsule.

20

Example 4

Tablets containing 500 mg clofibrate by itself or in combination with 10 mg BMS 201,038 may be employed in separate dosage forms or combined in a single capsule form.

25

Examples 5, 6 and 7

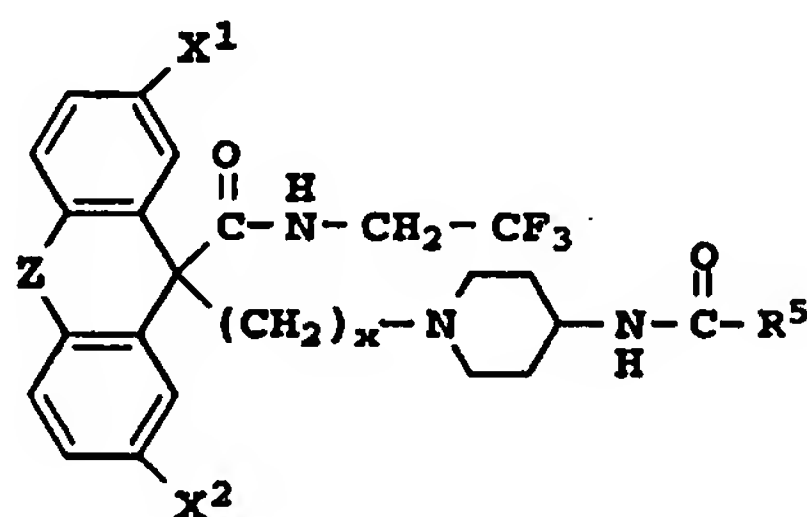
Ciprofibrate, bezafibrate, gemfibrozil alone or in combination with an MTP inhibitor may also be prepared in a manner described hereinbefore in Examples 1 to 3.

What is claimed is:

1. A method for inhibiting or treating a disease associated with acid-lipase deficiency in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of an MTP inhibitor.

2. The method as defined in Claim 1 wherein the MTP inhibitor is employed in combination with another type of cholesterol lowering drug.

3. The method as defined in Claim 2 wherein the MTP inhibitor has the structure



including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;

X¹ and X² are independently selected from H or halo;

x is an integer from 2 to 6;

R⁵ is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each R⁵ group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different.

4. The method as defined in Claim 3 where in the MTP inhibitor Z is a bond.

5. The method as defined in Claim 3 where the MTP inhibitor is a piperidine N-oxide.

6. The method as defined in Claim 3 where in the MTP inhibitor (CH₂)_x is optionally substituted with 1, 2 or 3 substituents which are the same or different and are alkyl or halo.

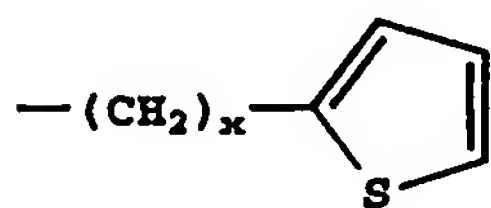
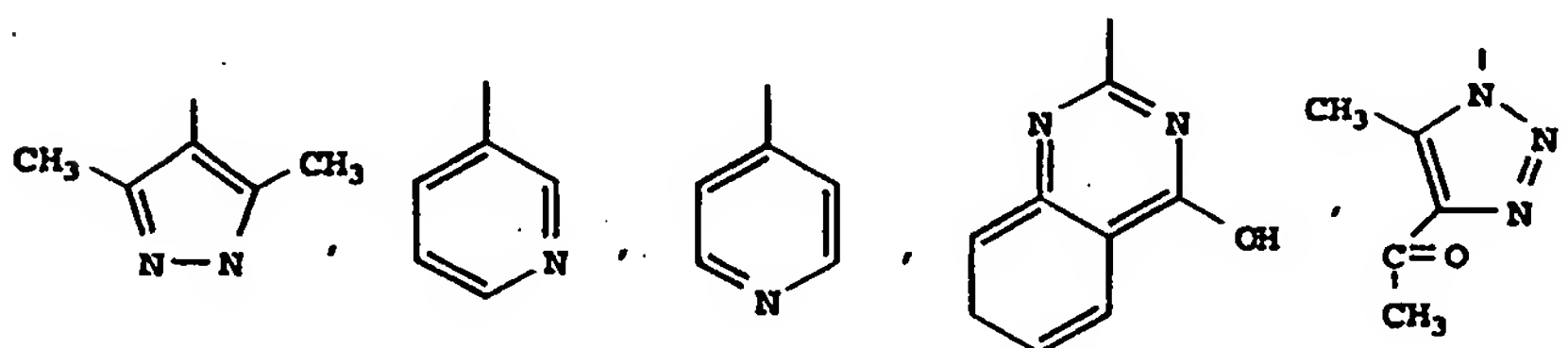
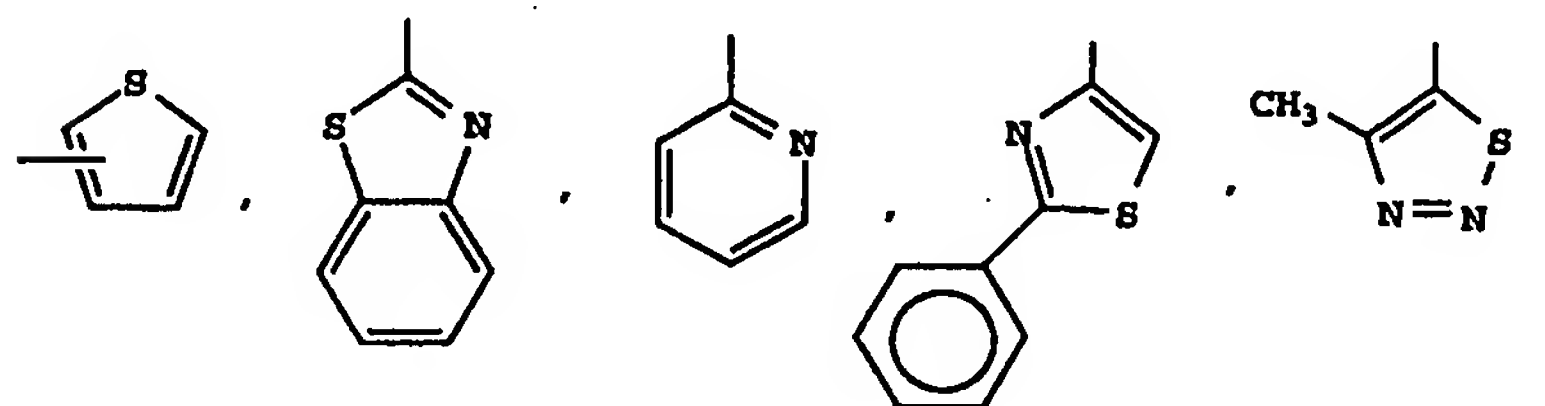
7. The method as defined in Claim 3 where in the MTP inhibitor R⁵ is substituted with 1, 2, 3 or 4

substituents which may be the same or different and are halogen, monocyclic heteroaryl, bicyclic heteroaryl, heteroarylalkyl, cycloheteroalkyl, alkyl, alkoxy, cycloalkyl, aryl, aryloxy, substituted aryl, arylalkyloxy, heteroaryloxy, amino, alkylamino, alkyl(aryl)amino, heteroarylamino, arylamino, alkylthio, arylthio, arylthioalkyl, heteroarylthio, arylsulfinyl or acyl.

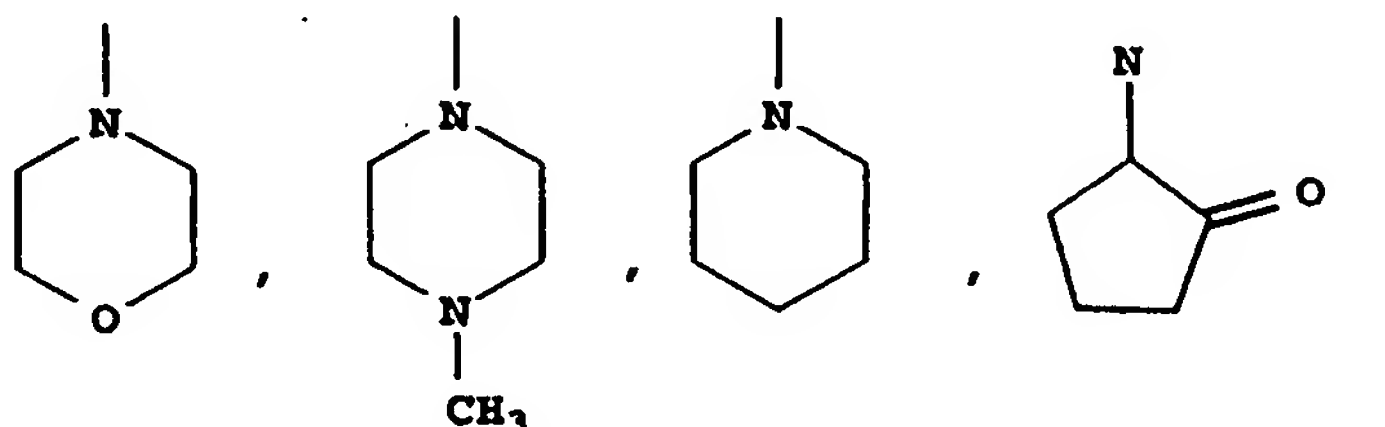
8. The method as defined in Claim 7 where in the MTP inhibitor the R⁵ includes a substituent attached to a carbon in the position adjacent to the carbon linked to a $\text{C}=\text{O}$.

9. The method as defined in Claim 7 where in the MTP inhibitor R⁵ is substituted with 1, 2, 3 or 4 of one or more of the following

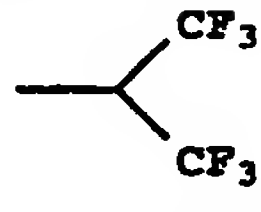
I, Cl, F, CF₃

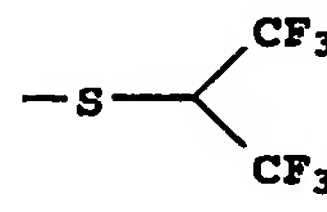


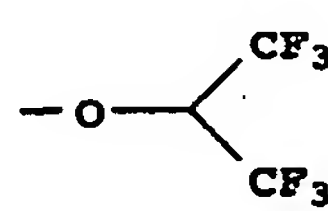
where x is 1 to 5

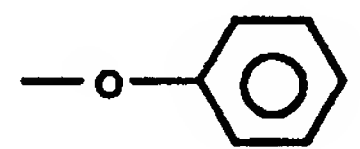
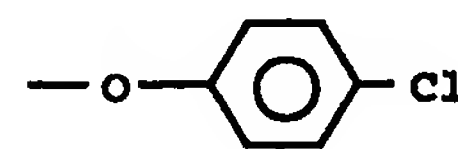


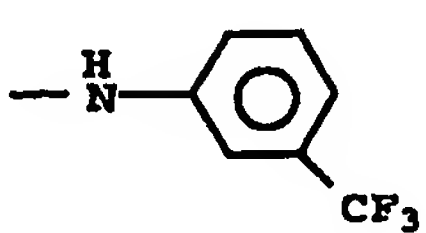
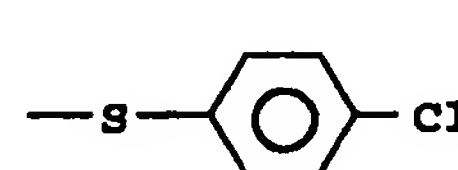
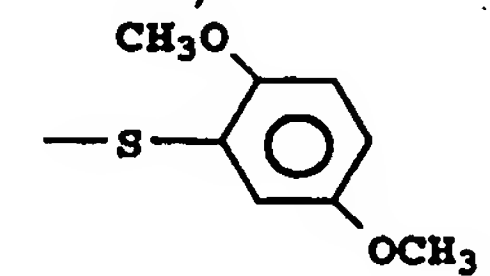
alkyl, phenyl, phenyl substituted with halo, alkyl, CF_3O ,

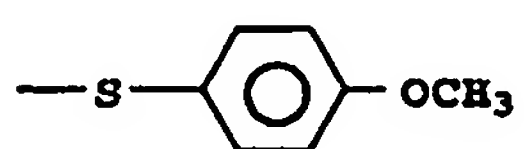
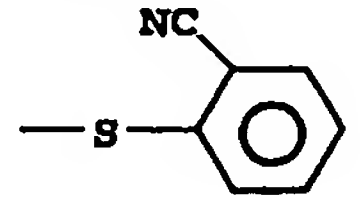
alkoxy, , CF_3 , or phenyl; $-\text{N}^{\text{H}}-(\text{CH}_2)_p\text{CF}_3-$ where p is 1 to 5, $-\text{N}(\text{CH}_3)\text{C}_6\text{H}_5$;

$-\text{S}-(\text{CH}_2)_p\text{CF}_3$ where p is 1 to 5, , $-\text{S}$ -alkyl,

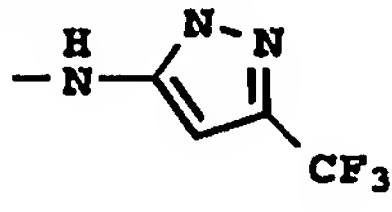
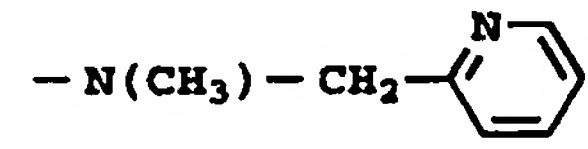
5 $-\text{S}-(\text{CH}_2)_p-\text{S}(=\text{O})_2\text{C}_6\text{H}_5$, , OCH_3 ;

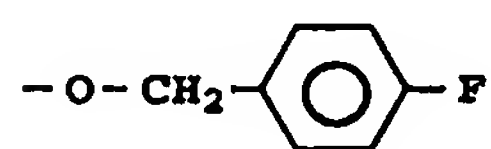

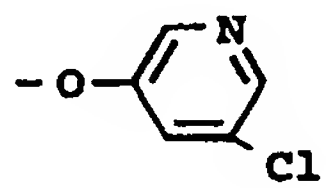
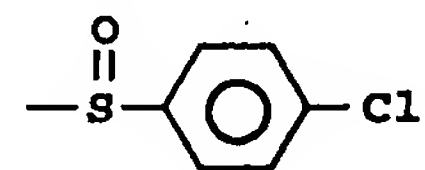
cyclohexyl, , ,

amino, , , ,

, ;

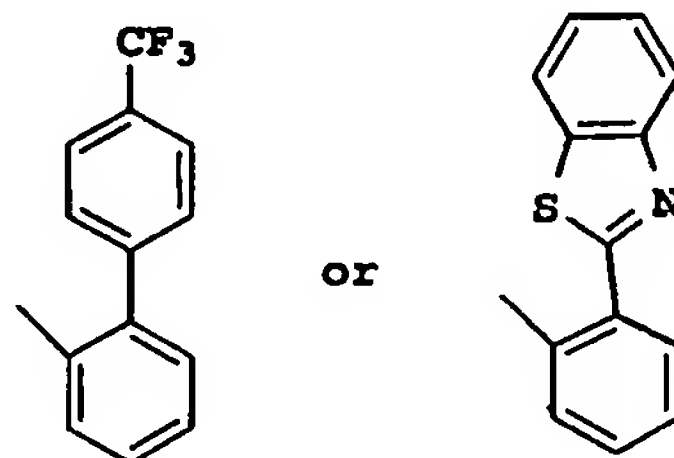
10 alkanoyl, alkoxycarbonyl, aroyl, heteroarylaminocarbonyl, arylalkyloxycarbonyl,

, ,

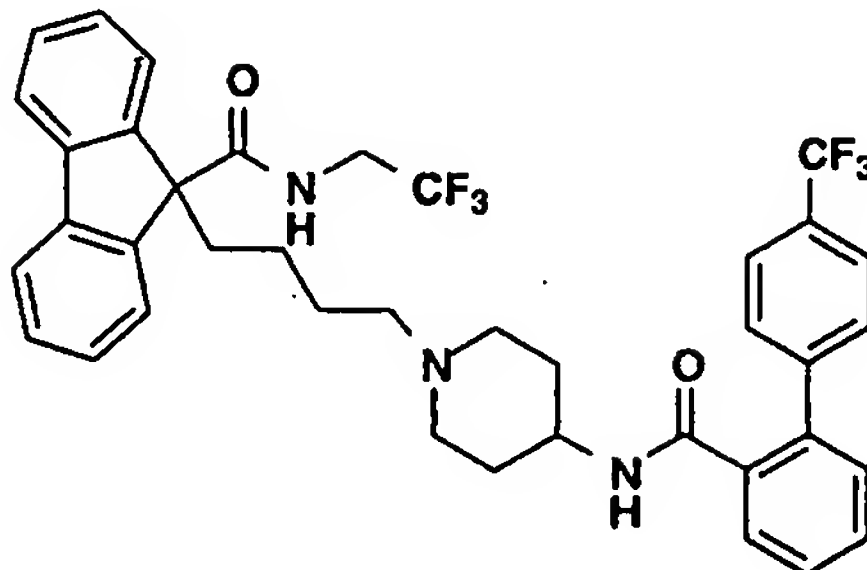
$-\text{CH}_2-\text{S}-\text{C}_6\text{H}_5$, , , , 

15 10. The method as defined in Claim 9 where in the MTP inhibitor R^5 is phenyl substituted with haloalkylphenyl or heteroaryl.

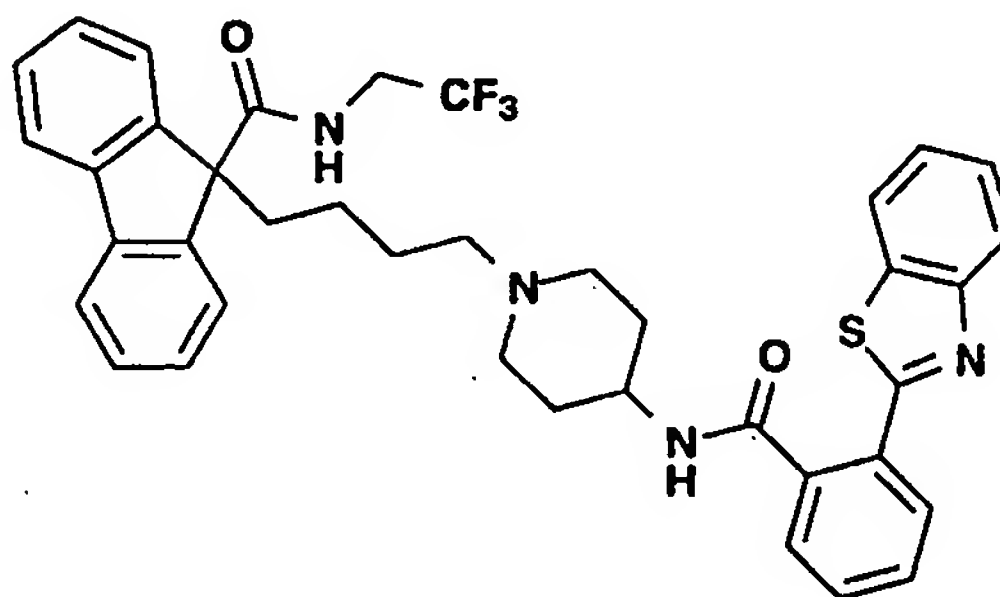
11. The method as defined in Claim 10 where in the MTP inhibitor R^5 is



12. The method as defined in Claim 9 where in the MTP inhibitor is

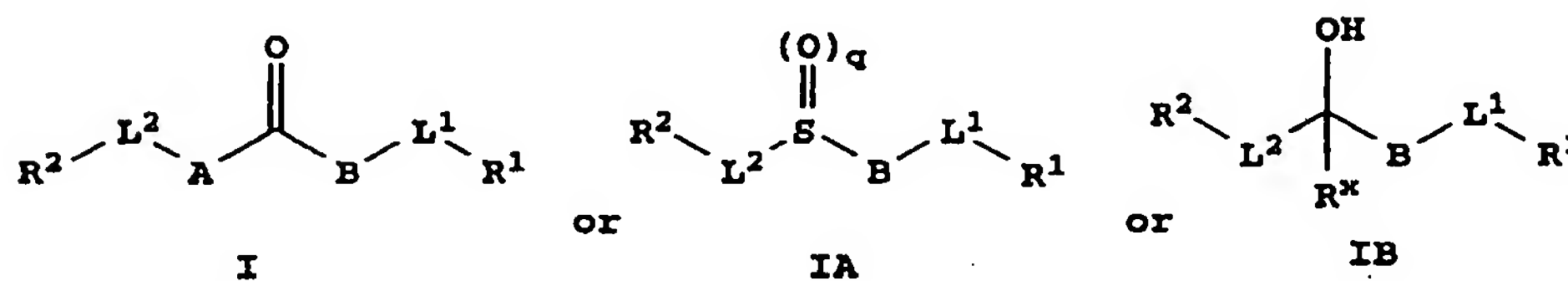


or



5

13. The method as defined in Claim 2 wherein the MTP inhibitor has the structure



10 including pharmaceutically acceptable salts thereof, N-oxides thereof,

wherein q is 0, 1 or 2;

A is (1) a bond;

(2) -O-; or



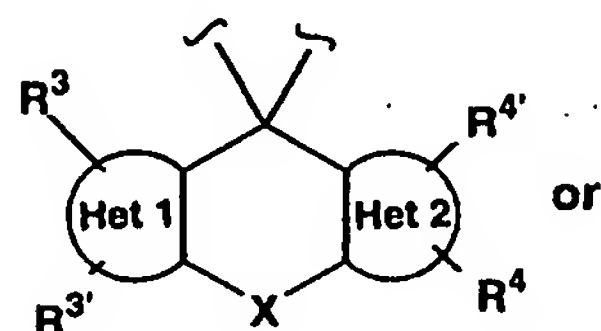
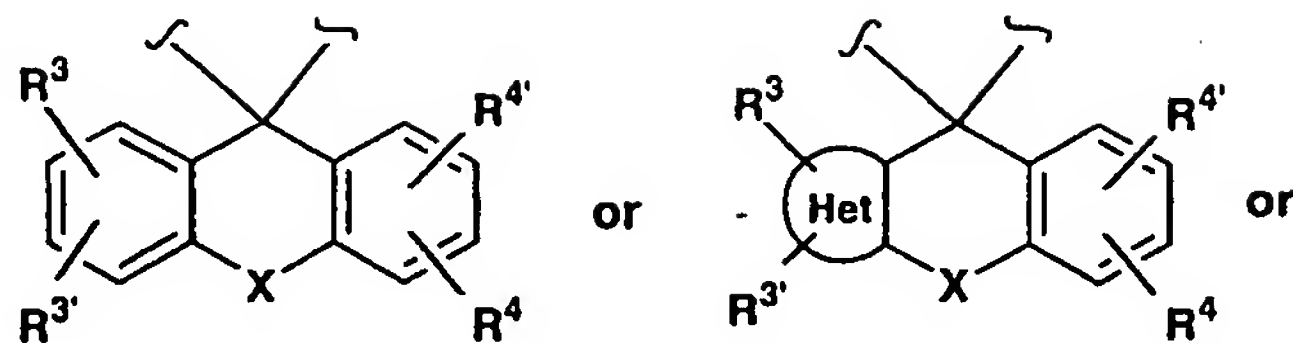
(3)

15

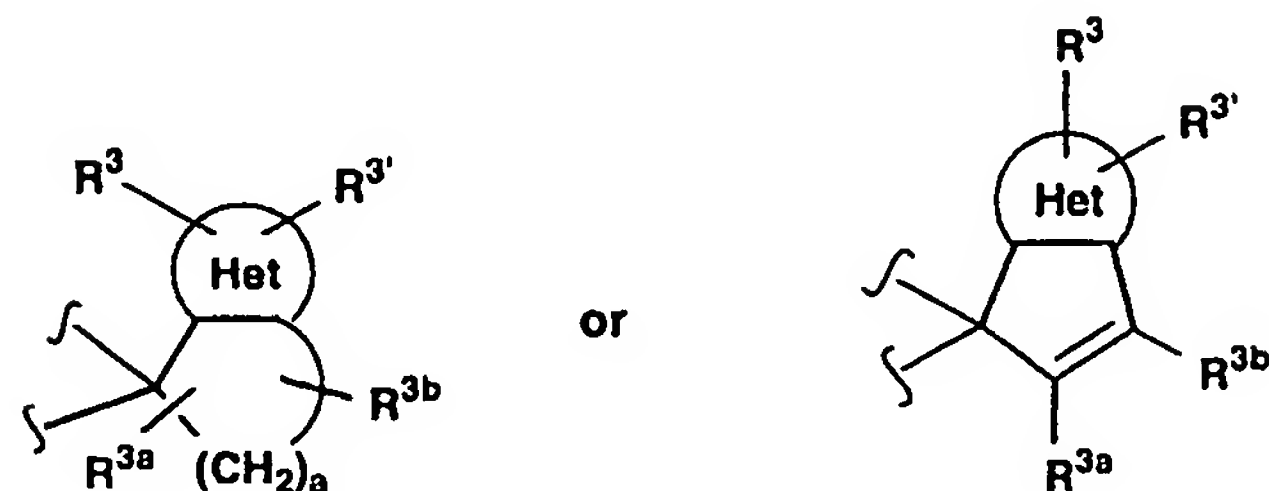
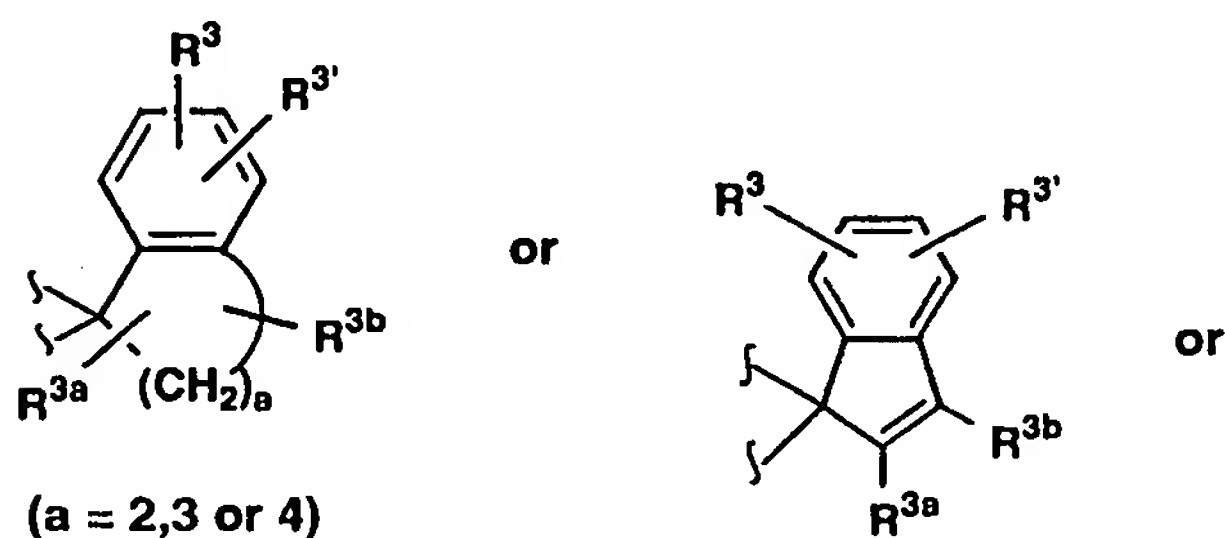
where R⁵ is H or lower alkyl, or R⁵ together with R² forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring;

B is a fluorenyl-type group of the structure

20



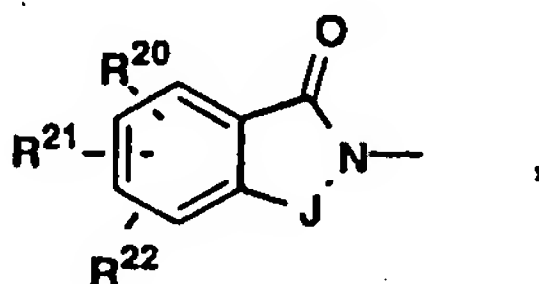
5 B is an indenyl-type group of the structure



10 R^x is H, alkyl or aryl;

R^1 is alkyl, alkenyl, alkynyl, alkoxy, (alkyl or aryl)₃Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino, aryl, arylalkyl, arylamino, arylsulfonylamino, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, -PO(R^{13})(R^{14}), (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy,

or cycloheteroalkylalkoxy); aminocarbonyl (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)₂alkyl (where the two aryl or alkyl substituents
 5 can be independently defined, or linked to one another to form a ring connected to L¹ (or L² in the case of R²) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L¹ (or L² in the case of R²) at the 4-position; the R¹ group may optionally be substituted with 1, 2, 3 or 4
 10 substituents, which can be any of the R³ or R¹ groups or alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxy carbonylamino, uriedo (where the uriedo
 15 nitrogens may optionally be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



where J is: CHR^{23} , $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$, $\text{—}\underset{\text{R}^{24}}{\text{CH}}\text{—}\underset{\text{R}^{25}}{\text{CH}}\text{—}$ or $\text{—}\overset{\text{O}}{\text{C}}=\text{C—}$;
 R^{24} R^{25} R^{24} R^{25}

R²³, R²⁴ and R²⁵ are independently hydrogen, alkyl, alkenyl,
 25 alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R²⁰, R²¹, R²² are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl,
 30 heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these substituents may either be directly attached to R¹, or attached via an alkylene at an open position;

R² is independently any of the groups set out for R¹, H, polyhaloalkyl, or cycloheteroalkyl, and may be

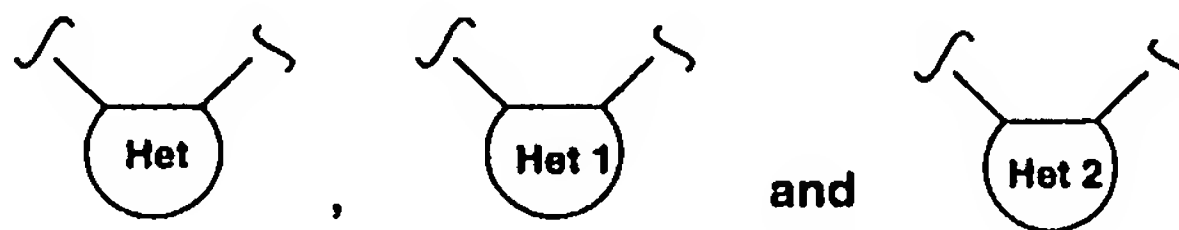
optionally substituted with one to four of any of the groups defined for R^3 or substituents defined for R^1 ;

L^1 is a linking group containing from 1 to 10 carbons in a linear chain including alkylene, alkenylene or alkynylene, which may contain, within the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group, an oxo group, and may be substituted with one to five alkyl or halo groups;

L^2 may be the same or different from L^1 and may independently be any of the L^1 groups set out above or a single bond;

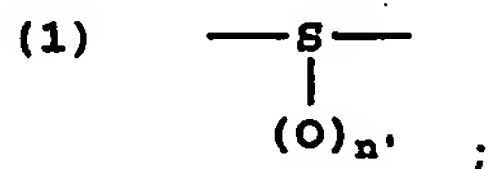
R^3 , $R^{3'}$, R^4 and $R^{4'}$ may be the same or different and are independently selected from H, halogen, CF_3 , haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar-, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

R^{3a} and R^{3b} are the same or different and are independently any of the R^3 groups except hydroxy, nitro, amino or thio;



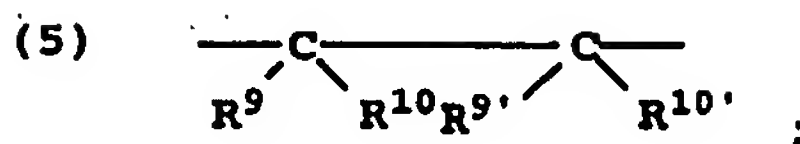
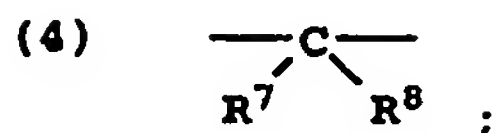
are the same or different and independently represent a 5 or 6 membered heteroaryl ring which contains 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides;

X is a bond, or is one of the following groups:

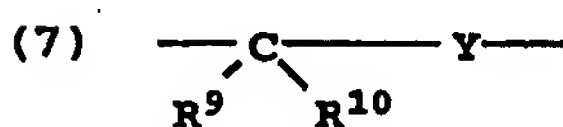
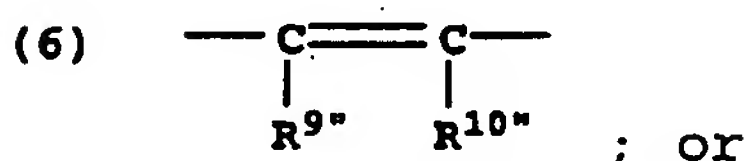




5



10



wherein

Y is O, N-R⁶ or S;

n' is 0, 1 or 2;

15 R⁶ is H, lower alkyl, aryl, -C(O)-R¹¹ or -C(O)-O-R¹¹;

R⁷ and R⁸ are the same or different and are independently H, alkyl, aryl, halogen, -O-R¹², or

R⁷ and R⁸ together can be oxygen to form a ketone;

20 R⁹, R¹⁰, R^{9'} and R^{10'} are the same or different and are independently H, lower alkyl, aryl or -O-R¹¹;

R^{9''} and R^{10''} are the same or different and are independently H, lower alkyl, aryl, halogen or -O-R¹¹;

25 R¹¹ is alky or aryl;

R¹² is H, alkyl or aryl;

14. The method as defined in Claim 13 wherein the



15. The method as defined in Claim 14 wherein A is
30 a bond.

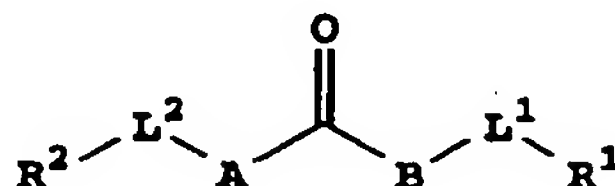
16. The method as defined in Claim 14 wherein A is -O-.

17. The method as defined in Claim 14 wherein A is

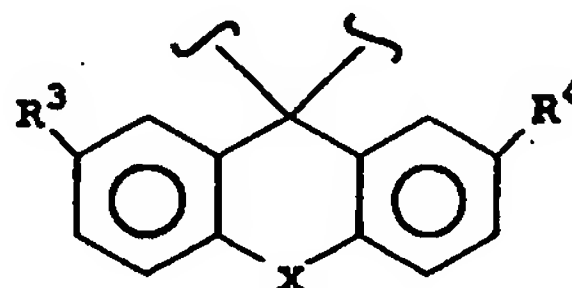


18. The method as defined in Claim 14 wherein B is a fluorenyl-type group.

19. The method as defined in Claim 14 having the formula

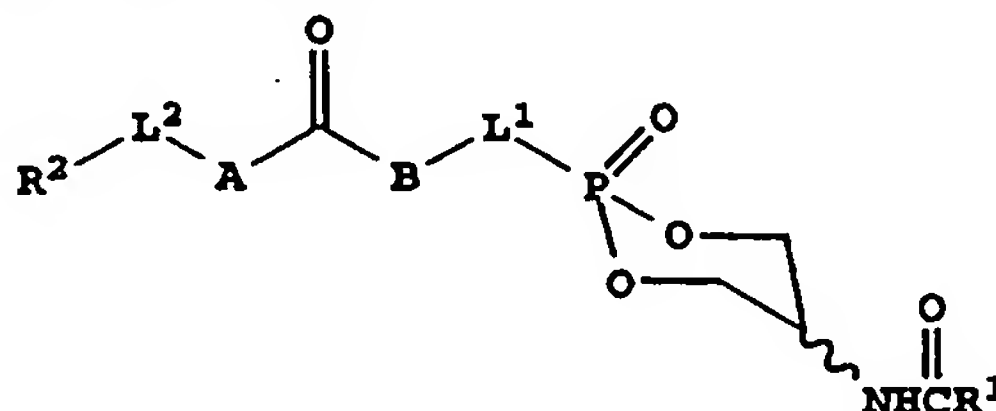


wherein B is



- 10 A is NH;
 X is a bond, oxygen or sulfur;
 R³ and R⁴ are the same or different and are H or F;
 R¹ is aryl, phenyl, heteroaryl, imidazolyl, pyridyl, cyclohexyl, PO(R¹³)(R¹⁴), heteroarylthio, benzthiazole-2-thio, imidazole-2-thio, alkyl, alkenyl or 1,3-dioxan-2-yl, wherein each of the above is optionally substituted;
 15 R² is alkyl, polyfluoroalkyl, alkenyl, aryl, phenyl, heteroaryl, imidazolyl or pyridyl, wherein each of the above is optionally substituted;
 20 L¹ is a chain containing 1 to 5 atoms in a linear chain;
 L² is a bond or lower alkylene.

20. The method as defined in Claim 1 wherein the MTP inhibitor has the structure



25 including pharmaceutically acceptable salts thereof, N-oxides thereof,

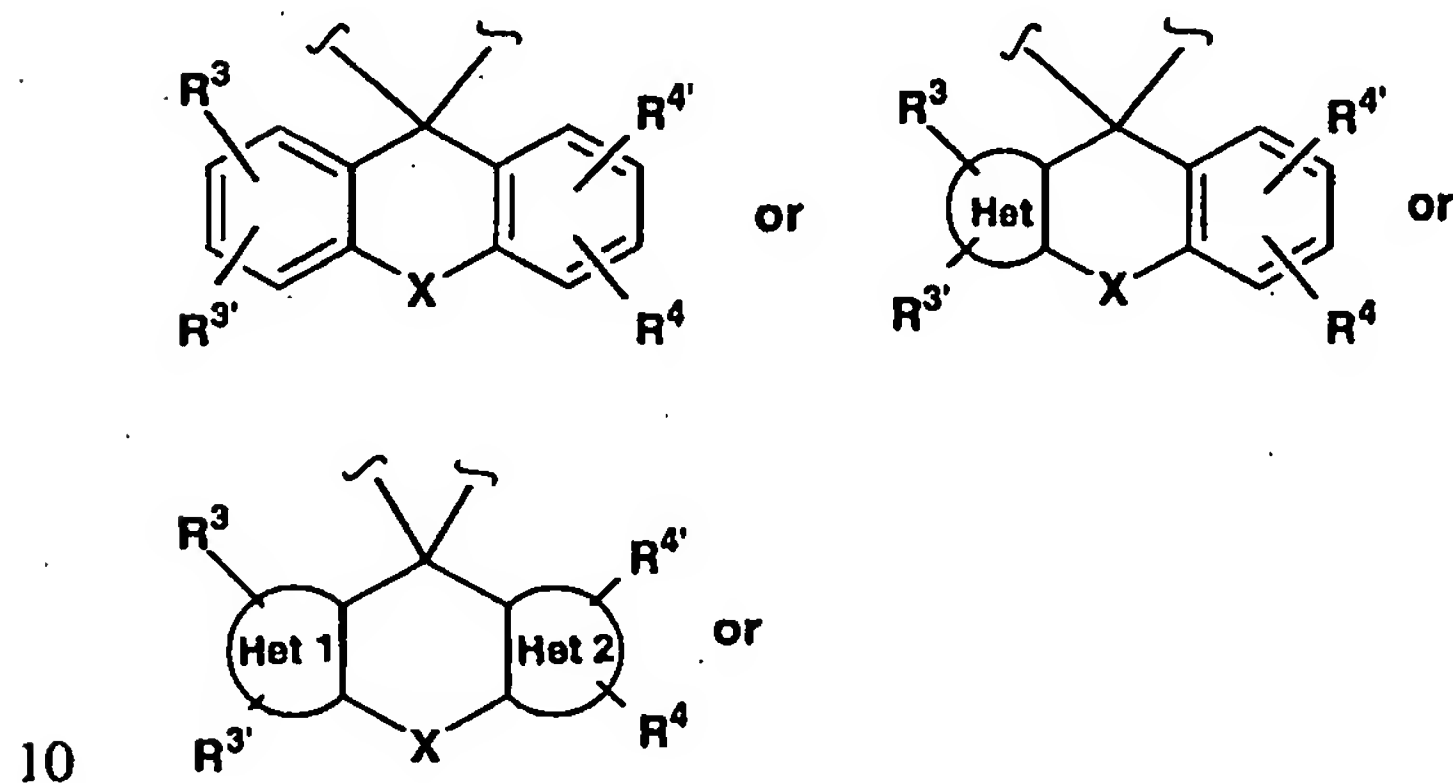
wherein

A is (1) a bond;

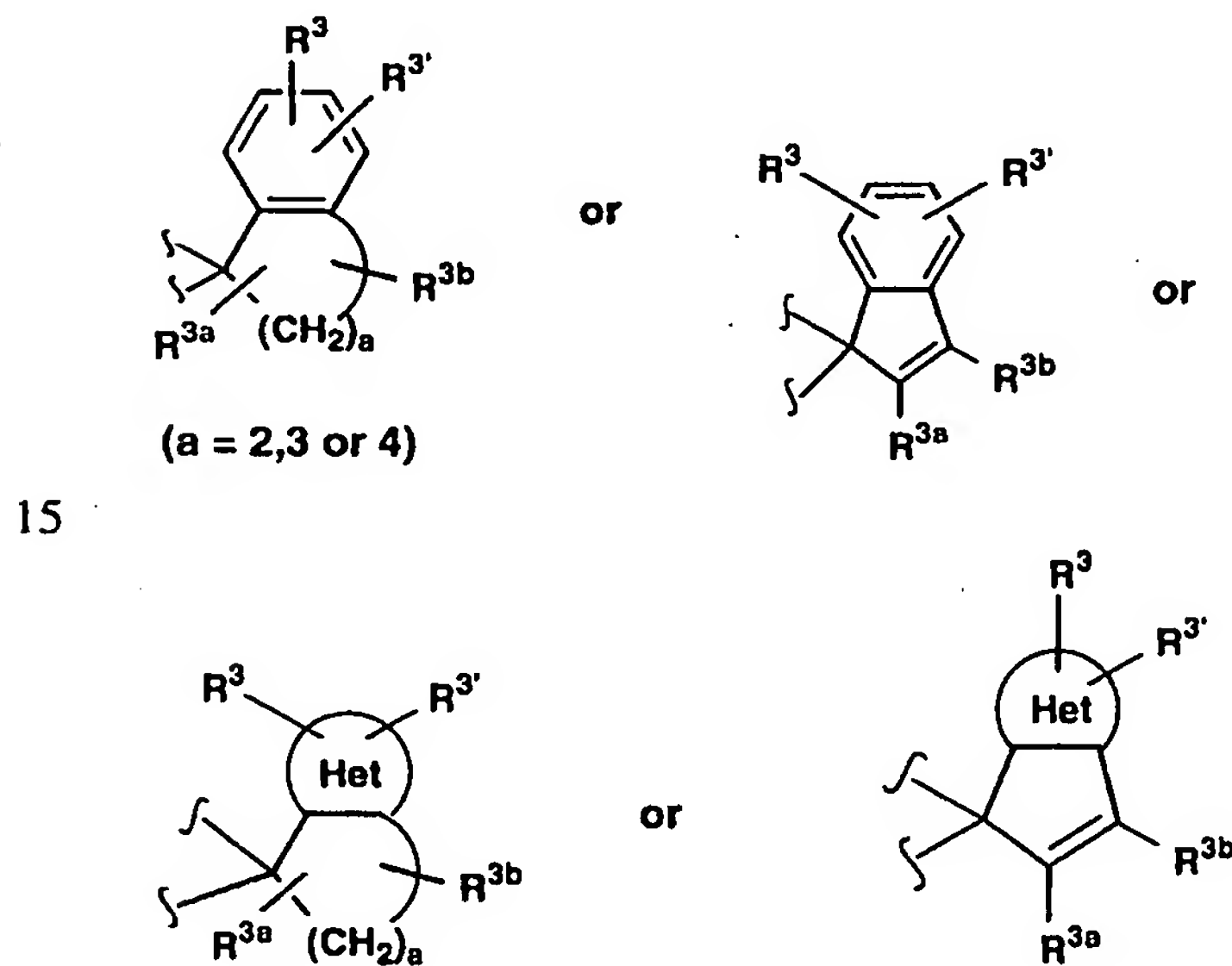
(2) $-O-$; or(3) $\begin{array}{c} \text{---N---} \\ | \\ R^5 \end{array}$

where R^5 is H or lower alkyl, or R^5 together with R^2 forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring;

B is a fluorenyl-type group of the structure:



B is an indenyl-type group of the structure



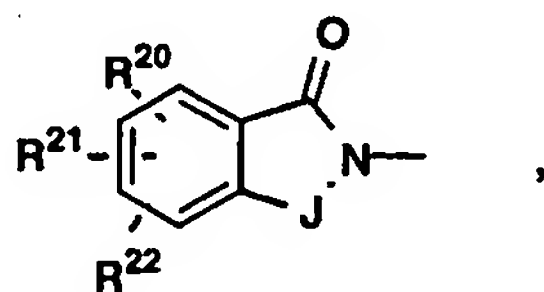
R^x is H, alkyl or aryl;

R^1 is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl,

20

- heteroarylalkyl, cycloalkyl, cycloalkylalkyl,
 polycycloalkyl, polycycloalkylalkyl, cycloalkenyl,
 cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl,
 polycycloalkenyl, polycycloalkenylalkyl,
- 5 heteroarylcarbonyl, amino, alkylamino, arylamino,
 heteroarylamino, cycloalkyloxy, cycloalkylamino, all
 optionally substituted through available carbon atoms with
 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl,
 haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl,
- 10 cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cyclohetero-
 alkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl,
 arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl,
 arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl,
 heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano,
- 15 amino, substituted amino, thiol, alkylthio, arylthio,
 heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl,
 arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl,
 alkynylaminocarbonyl, alkylaminocarbonyl,
 alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy,
- 20 alkylcarbonyl-amino, arylcarbonylamino, arylsulfinyl,
 arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl,
 arylsulfonylamino, heteroarylcarbonylamino,
 heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl,
 alkylsulfinyl;
- 25 R^2 is alkyl, alkenyl, alkynyl, alkoxyl, (alkyl or
 aryl)₃Si (where each alkyl or aryl group is independent),
 cycloalkyl, cycloalkenyl, substituted alkylamino,
 substituted arylalkylamino, aryl, arylalkyl, arylamino,
 aryloxy, heteroaryl, heteroarylamino, heteroaryloxy,
- 30 arylsulfonylamino, heteroarylsulfonylamino, arylthio,
 arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl,
 alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, hetero-
 arylsulfonyl, $-PO(R^{13})(R^{14})$, (where R^{13} and R^{14} are
 independently alkyl, aryl, alkoxy, aryloxy, heteroaryl,
- 35 heteroarylalkyl, heteroaryloxy, heteroarylalkoxy,
 cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy,
 or cycloheteroalkylalkoxy); aminocarbonyl (where the amino

may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)₂alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring connected to L¹ (or L² in the case of R²) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L¹ (or L² in the case of R²) at the 4-position; the R² group may optionally be substituted with 1, 2, 3 or 4 substituents, which can be any of the R³ or R¹ groups or alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxy carbonylamino, heteroaryloxy carbonylamino, uriedo (where the uriedo nitrogens may optionally be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



where J is: CHR^{23} , $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}$, $\text{--}\underset{\text{R}^{24}}{\text{CH}}\text{--}\underset{\text{R}^{25}}{\text{CH}}\text{--}$ or $\text{--}\underset{\text{R}^{24}}{\text{C}}=\underset{\text{R}^{25}}{\text{C}}\text{--}$;

R²³, R²⁴ and R²⁵ are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R²⁰, R²¹, R²² are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkyl-alkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these substituents may either be directly attached to R¹, or attached via an alkylene at an open position;

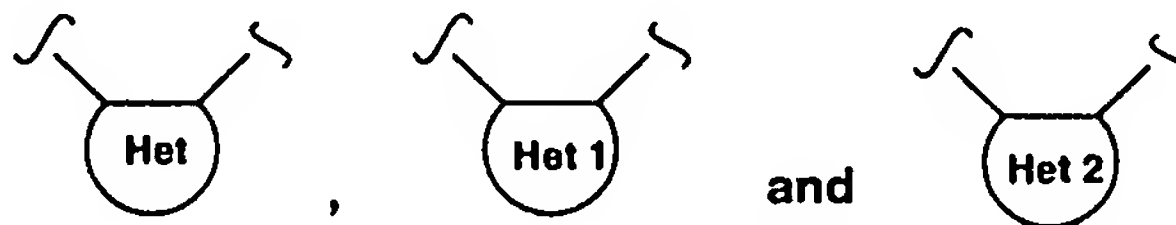
L¹ is a linking group containing from 1 to 10 carbons in a linear chain including alkylene, alkenylene or

alkynylene, which may contain, within the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group, an oxo group, and may be substituted with one to five alkyl or halo groups;

5 L^2 may be the same or different from L^1 and may independently be any of the L^1 groups set out above or a single bond;

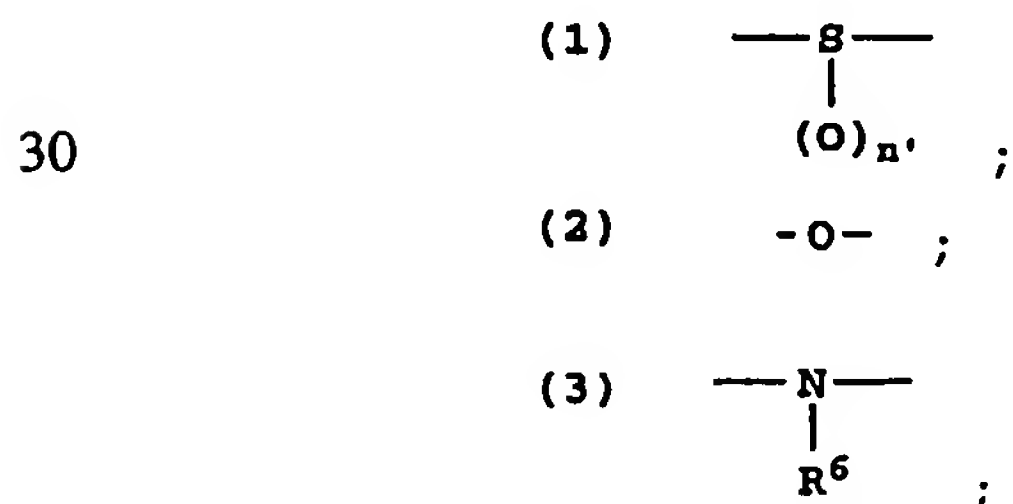
R^3 , $R^{3'}$, R^4 and $R^{4'}$ may be the same or different and are independently selected from H, halogen, CF_3 , haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, 10 alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar-, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, 15 Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

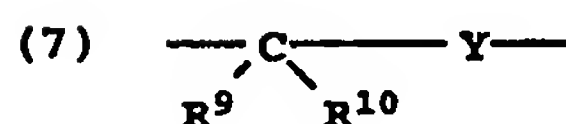
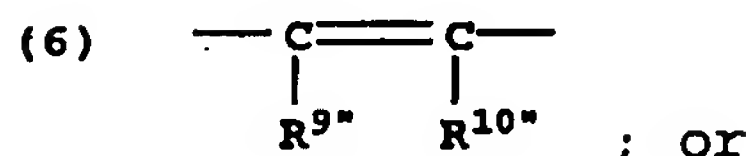
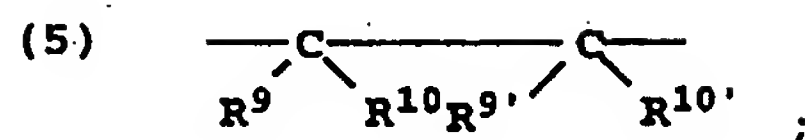
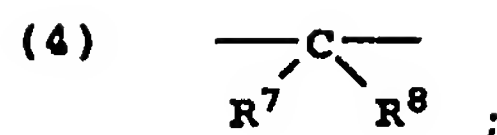
R^{3a} and R^{3b} are the same or different and are 20 independently any of the R^3 groups except hydroxy, nitro, amino or thio;



are the same or different and independently represent a 5 or 6 membered heteroaryl ring which contains 1, 2, 3 or 4 25 heteroatoms in the ring which are independently N, S or O; and including N-oxides;

X is a bond, or is one of the following groups:





wherein

10 Y is O, N-R⁶ or S;

n' is 0, 1 or 2;

R⁶ is H, lower alkyl, aryl, -C(O)-R¹¹ or
-C(O)-O-R¹¹;

15 R⁷ and R⁸ are the same or different and are
independently H, alkyl, aryl, halogen, -O-R¹², or

R⁷ and R⁸ together can be oxygen to form a ketone;

R⁹, R¹⁰, R^{9'} and R^{10'} are the same or different and
are independently H, lower alkyl, aryl or -O-R¹¹;

20 R^{9''} and R^{10''} are the same or different and are
independently H, lower alkyl, aryl, halogen or
-O-R¹¹;

R¹¹ is alkyl or aryl;

R¹² is H, alkyl or aryl.

21. The method as defined in Claim 1 wherein the
25 disease to be treated is Wolman disease.

22. The method as defined in Claim 1 wherein the
disease to be treated is cholesteryl ester storage disease.

23. The method as defined in Claim 2 wherein the
other cholesterol lowering drug is an HMG CoA reductase
30 inhibitor, a squalene synthetase inhibitor, a fibric acid
derivative, probucol, a bile acid sequestrant, nicotinic
acid or neomycin.

24. The method as defined in Claim 23 wherein the HMG CoA reductase inhibitor is pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin.

25. The method as defined in Claim 2 wherein the
5 cholesterol lowering drug is a fibric acid derivative which is gemfibrozil, fenofibrate, clofibrate, bezafibrate, ciprofibrate, clinofibrate, probucol, gemfibrozil, dextrothyroxine or its sodium salt, colestipol or its hydrochloride, cholestyramine, nicotinic acid, neomycin,
10 p-aminosalicylic acid or aspirin.

26. The method as defined in claim 2 wherein the MTP inhibitor is present in a weight ratio to the other cholesterol lowering drug (where present) within the range from about 500:1 to about 1:500.

15 27. The method as defined in Claim 1 wherein the MTP inhibitor lowers plasma LDL-cholesterol to at least 50% of normal LDL blood levels, and lowers triglycerides to at least 50% of normal triglyceride blood levels.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/00619

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/445, 31/425, 31/22

US CL :514/325, 367, 546

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/325, 367, 546

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: compounds and methods of use

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| Y | US 4,346,227 A (TERAHARA et al.) 24 August 1982, See entire document. | 2-27 |
| Y | EP 0 643 057 A1 (BRISTOL-MEYERS SQUIBB COMPANY) 15 March 1995, See entire document. | 1-27 |



Further documents are listed in the continuation of Box C.



See patent family annex.

| | |
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| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
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| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

25 APRIL 1998

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